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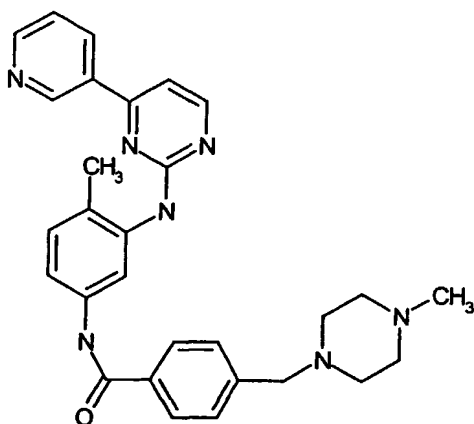
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(54) Title: **PYRIDYLPYRIMIDINE DERIVATIVES AS EFFECTIVE COMPOUNDS AGAINST PRION DISEASES**



Compound 53 (GleevecTM)

(57) Abstract: The present invention relates to pyridylpyrimidine derivatives of the general formula (I): wherein R represents hydrogen or methyl and Z represents nitrogen containing functional groups, the use of the pyridylpyrimidine derivatives as pharmaceutically active agents, especially for the prophylaxis and/or treatment of prion infections and prion diseases, as well as compositions containing at least one pyridylpyrimidine derivative and/or pharmaceutically acceptable salt thereof. Furthermore, the present invention is directed to methods for preventing and/or treating prion infections and prion diseases using said pyridylpyrimidine derivatives. Human cellular protein kinases, phosphatases and cellular signal transduction molecules are disclosed as targets for detecting, preventing and/or treating prion infections and diseases, especially BSE, vCJD, or CJD, which can be inhibited by the inventive pyridylpyrimidine derivatives.

Pyridylpyrimidine derivatives as effective compounds against prion infections and prion diseases

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Specification

The present invention relates to pyridylpyrimidine derivatives, the use of the pyridylpyrimidine derivatives as pharmaceutically active agents, especially for the prophylaxis and/or treatment of prion infections and prion diseases, as well as compositions containing at least one pyridylpyrimidine derivative and/or pharmaceutically acceptable salt thereof, and methods for preventing and/or treating prion infections and prion diseases. Furthermore, human cellular protein kinases, phosphatases and cellular signal transduction molecules are disclosed as targets for detecting, preventing and/or treating prion infections and diseases, especially BSE, vCJD, or CJD.

Background of the invention

Pyridylpyrimidine derivatives are known from WO 9509851 as effective compounds for chemotherapy of tumors, from WO 9509853, EP-A-0 588 762, WO 9509847, WO 9903854, and EP-B-0 564 409 as effective compounds for treatment of tumors. Furthermore, EP-B-0 564 409 discloses the use of said compounds in the treatment of arteriosclerosis and Exp. Opin. Ther. Patents, 1998, 8(12), 1599-1625 describes the use of pyridylpyrimidine derivatives, especially of GleevecTM, the Novartis compound CGP 57148, as tyrosine kinase inhibitors in cancer treatment.

Prions are infectious agents which do not have a nucleic acid genome. It seems that a protein alone is the infectious agent. A prion has been defined as "small proteinaceous infectious particle which resists inactivation by procedures that modify nucleic acids". The discovery that proteins alone can transmit an infectious disease has come as a considerable surprise to the scientific community. Prion diseases are often called "transmissible spongiform encephalopathies", because of the post mortem appearance of the brain with large vacuoles in the cortex and cerebellum. Probably most mammalian species develop these diseases. Prion diseases are a group of neurodegenerative disorders of humans and animals and the prion diseases can manifest as sporadic, genetic or infectious disorders. Examples for prion diseases acquired

by exogenous infection are the Bovine spongiform encephalitis (BSE) of cattle and the new variant of Creutzfeld-Jakob disease (vCJD) caused by BSE. Further examples include kuru, Gerstmann-Sträussler-Scheinker disease of humans as well as scrapie of animals. For many years, the prion diseases were thought to be caused by viruses despite intriguing evidence to the contrary. The unique characteristic common to all of these disorders, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant metabolism of the prion protein (PrP). In many cases, the cellular prion protein (PrP^c) ["c" refers to cellular] is converted into the scrapie isoform (PrP^{Sc}) ["Sc" refers to Scrapie] by a posttranslational process that involves a conformational change. Often, the human prion diseases are transmissible to experimental animals and all of the inherited prion diseases segregate with PrP gene mutations.

These prion diseases in animals and humans have a long incubation period and a long clinical course, and are always fatal leading via decerebration to death within an average period of 7 months (CJD). Neuropathological features consist of neuronal vacuolization, neuronal death and gliosis with hyperastrocytosis. The precise diagnosis of transmissible neurodegenerative diseases can be established only by the examination of the central nervous system after biopsy or autopsy.

Clinical symptoms of the disease are progressive dementia, myoclonus and prominent ataxia with the additional clinical features of dysautonomia and delirious psychomotor excitement and with relatively preserved verbal responses.

Between 1980 and, roughly, 1996, about 750,000 cattle infected with BSE were slaughtered for human consumption in Great Britain (Anderson, R. M. *et al. Nature* 382, 779-788, 1996; Ferguson, N. M., Donnelly, C. A., Woolhouse, M. E. J. & Anderson, R. M. *Phil. Trans. R. Soc. Lond. B* 352, 803-838, 1997). The annual incidence of vCJD (3, 10, 10, 18, 14 and 33 deaths in 1995-2000, respectively) can be interpreted as a first sign of a steady or exponential increase over the next years. The suggestion by the European Union Scientific Steering Committee that up to 500,000 people could have been exposed to BSE from a single infected bovine has fuelled speculation that millions of consumers are at risk.

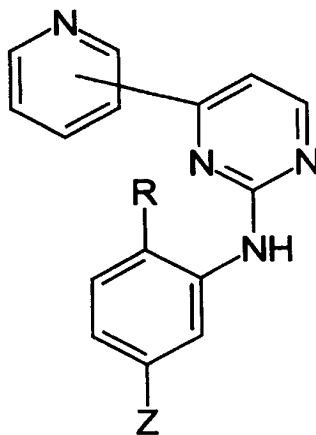
Recent findings demonstrate that the pathogenic PrP^{Sc} of vCJD can be found in the lymph system (e.g. tonsils, lymph nodes) in humans suggesting a high risk of horizontal spread via lymph and/or blood transmission, dramatically increasing the number of people at risk.

- The medical need in prion diseases today can be clearly defined as the establishment of a diagnostic system, that can detect the disease as early as possible in living humans and/or animals, to estimate the medical need for the treatment in the future and to identify the infected animals to remove them from the food chain. The medical need for prion diseases in the future (approximately starting in 5-10 years) will be medical treatment that inhibits the disease symptoms, the manifestation and/or progression of the disease.
- It is object of the present invention to provide novel and also known compounds which can be used as pharmaceutically active agents, especially for prophylaxis and/or treatment of prion infections and prion diseases, methods wherein said compounds are used in order to treat prion infections and prion diseases and compositions containing at least one inventive compound and/or pharmaceutically acceptable salt thereof as a pharmaceutically active ingredient.

The object of the present invention is solved by the teaching of the independent claims. Further advantageous features, aspects and details of the invention are evident from the dependent claims, the description, the examples, and the figures of the present application.

Description of the invention

One aspect of the present invention is related to compounds of the general formula (I):



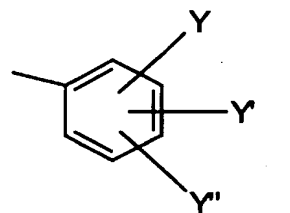
wherein:

R represents hydrogen or methyl;

Y, Y', Y'' are independently of each other -H, -F, -Cl, -Br, -I, -CH₂F, -CH₂Cl, -CH₂Br, -CH₂I, -OH, -OCH₃, -CH₃, -CN, -OCF₃, 4-methylpiperazin-1-yl-methyl, -C(CH₃)=N-NH-C(NH)-NH₂;

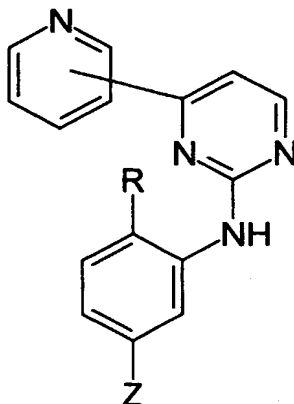
Z represents -NO₂, -NH₂, -NH-CO-X, -NH-CS-X, -NH-CO-NH-X,
5 -NH-SO₂-X;

X represents thiophenyl, cyclohexyl, isoquinolinyl, naphthyl, quinolinyl, cyclopentyl, pyridinyl, naphthyridinyl, or



and pharmaceutically acceptable salts thereof.

Another aspect of the present invention relates to the use of compounds of the
10 general formula (I):



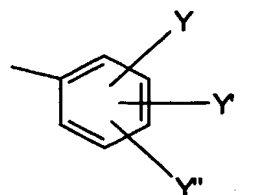
wherein:

R represents hydrogen or methyl;

Y, Y', Y'' are independently of each other -H, -F, -Cl, -Br, -I, -CH₂F, -CH₂Cl, -CH₂Br, -CH₂I, -OH, -OCH₃, -CH₃, -CN, -OCF₃, 4-
15 methylpiperazin-1-yl-methyl, -C(CH₃)=N-NH-C(NH)-NH₂;

Z represents -NO₂, -NH₂, -NH-CO-X, -NH-CS-X, -NH-CO-NH-X, -NH-SO₂-X;

X represents thiophenyl, cyclohexyl, isoquinolinyl, naphthyl, quinolinyl, cyclopentyl, pyridinyl, naphthyridinyl, or



and pharmaceutically acceptable salts thereof as pharmaceutically active agents, especially for prophylaxis and/or treatment of infectious diseases, or in a more general sense, for prophylaxis and/or treatment of neurodegenerative diseases.

5 Thus, one embodiment of the present invention disclosed herein is directed to a method for preventing and/or treating infections and/or diseases associated with said infections in an individual. Said method comprises administering to the individual an amount of at least one compound according to general formula (I) and/or pharmaceutically acceptable salts thereof effective to prevent and/or treat
10 said infections and/or diseases. Most preferred is the administration of a compound 53.

As revealed for the first time herein, the present invention discloses the use of compounds of the general formula (I) for the prophylaxis and/or treatment of prion
15 infections and prion diseases. As described above, said pyridylpyrimidine derivatives have first of all been used in tumor therapy. The Novartis compound GleevecTM also known as GlivecTM, CGP-57148B, imatinib mesylate, STI-571, STI-571A, CAS 152459-95-5, or 4-((Methyl-1-piperazinyl)methyl)-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate, has been
20 registered in many countries as anticancer drug. This GleevecTM compound (compound 53) is also the most active one in the indication prion diseases.

The name "prion" is used to describe the causative agents which underlie the transmissible spongiform encephalopathies. A prion is proposed to be a novel
25 infectious particle that differs from viruses and viroids. It is composed solely of one unique protein that resists most inactivation procedures such as heat, radiation, and proteases. The latter characteristic has led to the term protease-resistant isoform of the prion protein. The protease-resistant isoform has been proposed to slowly catalyze the conversion of the normal prion protein into the
30 abnormal form.

The term "isoform" in the context of prions means two proteins with exactly the same amino acid sequence that are folded into molecules with dramatically different tertiary structures. The normal cellular isoform of the prion protein
35 (PrP^C) has a high α -helix content, a low β -sheet content, and is sensitive to protease digestion. The abnormal, disease-causing isoform (PrP^{Sc}) has a lower α -helix content, a much higher β -sheet content, and is much more resistant to protease digestion.

Moreover, in a more general sense, the present invention is concerned with the prophylaxis and/or treatment of neurodegenerative diseases. For example, Alzheimer is a well-known neurodegenerative disease.

- 5 Preferred are the compounds wherein R represents hydrogen. Also preferred are compounds wherein Z represents $-\text{NH}-\text{CO}-\text{X}$ or $-\text{NH}-\text{SO}_2-\text{X}$ and/or wherein Y, Y', Y'' are independently of each other $-\text{H}$, $-\text{F}$, $-\text{Cl}$, $-\text{CH}_2\text{F}$, $-\text{CH}_2\text{Cl}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{CN}$, $-\text{OCF}_3$, or a 4-methylpiperazin-1-yl-methyl residue.
- 10 Also preferred are the following pyridylpyrimidine derivatives selected from the group comprising:
- Compound 1: (3-Nitrophenyl)-(4-pyridin-3-yl-pyrimidin-2-yl)-amine;
 - Compound 2: (3-Aminophenyl)-(4-pyridin-3-yl-pyrimidin-2-yl)-amine;
 - Compound 3: (5-Amino-2-methylphenyl)-(4-pyridin-3-yl-pyrimidin-2-yl)-
15 amine;
 - Compound 4: 4-Chloromethyl-N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
 - Compound 5: 4-Chloromethyl-N-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
 - 20 Compound 6: 4-(4-Methylpiperazin-1-ylmethyl)-N-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
 - Compound 7: Thiophene-3-carboxylic acid [4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-amide;
 - Compound 8: 4-Chloro-N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-
25 phenyl]-benzamide;
 - Compound 9: 4-Chloro-N-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
 - Compound 10: 3,4,5-Trimethoxy-N-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
 - 30 Compound 11: 4-Cyano-N-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
 - Compound 12: 4-Methoxy-N-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
 - Compound 13: 4-Chloro-N-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-
35 benzenesulfonamide;
 - Compound 14: Thiophene-3-carboxylic acid [3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;

- Compound 15: 3,5-Dimethoxy-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 16: 3,4,5-Trimethoxy-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 5 Compound 17: 4-Cyano-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 18: 4-Methoxy-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 19: 4-Chloro-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;
- 10 Compound 20: Thiophene-3-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Compound 21: 3,5-Dimethoxy-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 15 Compound 22: 4-Trifluoromethoxy-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 23: Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Compound 24: Cyclohexanecarboxylic acid [3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 20 Compound 25: Isoquinoline-5-sulfonic acid [4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Compound 26: Isoquinoline-5-sulfonic acid [3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 25 Compound 27: (5-Nitro-2-methylphenyl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine;
- Compound 28: (5-Amino-2-methylphenyl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine;
- Compound 29: 3,4,5-Trimethoxy-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 30 Compound 30: 4-Cyano-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 31: (3-Aminophenyl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine;
- Compound 32: 4-Chloro-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 35 Compound 33: Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Compound 34: 4-Cyano-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

- Compound 35: 4-Chloro-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;
- Compound 36: 4-Methoxy-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 5 Compound 37: 4-Chloro-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 38: Cyclohexanecarboxylic acid [3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Compound 39: 3,5-Dimethoxy-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 10 Compound 40: (5-Amino-2-methylphenyl)-(4-pyridin-4-yl-pyrimidin-2-yl)-amine;
- Compound 41: Thiophene-3-carboxylic acid [3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 15 Compound 42: 4-Chloro-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;
- Compound 43: 4-Chloro-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 44: (3-Aminophenyl)-(4-pyridin-4-yl-pyrimidin-2-yl)-amine;
- 20 Compound 45: (3-Nitrophenyl)-(4-pyridin-4-yl-pyrimidin-2-yl)-amine;
- Compound 46: 4-Trifluoromethoxy-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 47: Isoquinoline-5-sulfonic acid [3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 25 Compound 48: 4-Methoxy-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 49: 4-Cyano-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 50: 3,4,5-Trimethoxy-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 30 Compound 51: 3,5-Dimethoxy-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 52: 3,4,5-Trimethoxy-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 35 Compound 53: 4-(4-Methylpiperazin-1-ylmethyl)-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide (GleevecTM);
- Compound 54: 4-Methyl-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide

- Compound 55: 4-Methoxy-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 56: 3,5-Dimethoxy-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 5 Compound 57: Naphthalene-2-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Compound 58: *N*-[3-(4-Pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 59: 4-Chloro-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 10 Compound 60: 4-Methoxy-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 61: 4-Chloro-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;
- Compound 62: Thiophene-2-carboxylic acid 3-(4-pyridin-2-yl-pyrimidin-2-yl-15 amino)-phenyl]-amide;
- Compound 63: Naphthalene-2-sulfonic-acid [3-(4-pyridin-2-yl-pyrimidin-2-yl-amino)-phenyl]-amide;
- Compound 64: Isoquinoline-5-sulfonic-acid [3-(4-pyridin-2-yl-pyrimidin-2-yl-amino)-phenyl]-amide;
- 20 Compound 65: Cyclopentanecarboxylic acid 3-(4-pyridin-2-yl-pyrimidin-2-yl-amino)-phenyl]-amide;
- Compound 66: Naphthalene-2-carboxylic acid [3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Compound 67: 4-Cyano-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-25 benzamide;
- Compound 68: 3,5-Dimethoxy-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 69: 4-Bromo-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 30 Compound 70: 4-Methyl-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 71: 4-Fluoro-*N*-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;
- Compound 72: 3,5-Dichloro-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-35 benzamide;
- Compound 73: *N*-[3-(4-Pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 74: 4-Chloromethyl-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

- Compound 75: 4-Methyl-*N*-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide
- Compound 76: 4-(4-Methylpiperazin-1-ylmethyl)-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 5 Compound 77: Naphthalene-2-carboxylic acid [3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Compound 78: 2-Methoxy-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 79: 2-Methoxy-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 10 Compound 80: 4-Methyl-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 81: 4-Methyl-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 15 Compound 82: *N*-[4-Methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 83: 1-(3,5-Diacetyl-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-urea;
- Compound 84: 1-{3,5-Bis-(amidinohydrazone)-phenyl}-3-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-urea;
- 20 Compound 85: *N*-[4-Methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-nicotinamide;
- Compound 86: *N*-[3-(4-Pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-nicotinamide;
- Compound 87: [1,8]Naphthyridine-2-carboxylic acid [3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 25 Compound 88: [1,8]Naphthyridine-2-carbothioic acid [3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Compound 89: 2-Methoxy-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 30 Compound 90: 4-Trifluoromethoxy-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Compound 91: 4-Methyl-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

35 and pharmaceutically active salts of these compounds.

Recent research has revealed how cells communicate with each other to coordinate the growth and maintenance of the multitude of tissues within the

human body. A key element of this communication network is the transmission of a signal from the exterior of a cell to its nucleus, which results in the activation or suppression of specific genes. This process is called signal transduction.

- 5 An integral part of signal transduction is the interaction of ligands, their receptors and intracellular signal transduction molecules. Ligands are messengers that bind to specific receptors on the surface of target cells. As a result of the binding, the receptors trigger the activation of a cascade of downstream signaling molecules, thereby transmitting the message from the exterior of the cell to its
- 10 nucleus. When the message reaches the nucleus, it initiates the modulation of specific genes, resulting in the production of RNA and finally proteins that carry out a specific biological function. Disturbed activity of signal transduction molecules may lead to the malfunctioning of cells and disease processes. Specifically, interference of the pathogenic PrP^{Sc} from prion diseases with
- 15 neuronal cells is necessary for the prion protein to induce its neuropathological features such as neuronal vacuolization, neuronal death and gliosis with hyperastrocytosis.

- A key element of this communication network is the transmission of a signal from the exterior of a cell to its nucleus, which results in the activation or suppression of specific genes. The human cellular protein kinases Abl and clk1 are two of the enzymes involved in said signal transduction process. As revealed herein said kinases Abl and clk1 serve as targets and are inhibited by the pyridylpyrimidine compounds of the general formula (I). It could be proved that prion infections
- 20 and/or prion diseases can be treated and also be prevented by the inhibition of said kinase Abl using the inventive pyridylpyrimidine derivatives. Inhibition of the kinase clk1 by said pyridylpyrimidine compounds can be used for the treatment of infections and diseases.

- 30 A microarray platform technology consisting of more than 1100 signal transduction cDNAs has been established. The technology is used for the identification of changes in RNA expression patterns as a result of the manipulation of the host cell by PrP^{Sc}. In addition, differential display techniques were used in order to pinpoint these changes to those enzymes which could be potential targets for drug
- 35 intervention.

Employing this predefined set of signal transduction relevant cDNAs on the filters, the expression pattern of signal transduction mRNAs in neuronal mouse cells

transfected with the pathogenic form of the prion protein (PrP^{Sc}) were compared with the same cells transfected with the non-pathogenic wild-type form (PrP^C) as a control. Interference of the PrP^{Sc} with the cellular signaling events is reflected in different gene expression when compared to the control cellular situation (PrP^C).

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Using this technology, the human cellular protein kinases FGF-R1 (also known as flg, Fl-1, Flt-2, or b-FGFR), Tkt (also known as CCK-2, DDR-2, or EDDR, EC Number 2.7.1.112), Abl (also known as c-abl), clk1, MKK7 (also known as SKK4, SAPKK4, SAPKK5, or JNKK2), LIMK-2, CaM-KI, JNK2 (also known as SAPK1a, SAPKalpha), CDC2 (also known as CDK1), PRK, the human cellular protein phosphatases PTP-SL (also known as MCP83), PTP-zeta, the cellular signal transduction molecules HSP86, and GPIR-1 were identified as potential anti-prion disease targets. Said cellular protein kinases, phosphatases and signal transduction molecules are found to be specifically up- or downregulated by PrP^{Sc} in relevant mouse neuronal cells.

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Surprisingly, it was found that the following human cellular targets are significantly up- or downregulated in prion infected cells:

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<u>target</u>	<u>regulation</u>
FGF-R1	3.6 fold stronger
Abl	5.6 fold stronger
MKK7	4.1 fold stronger
CDC2	2.0 fold weaker
25 Tkt	2.1 fold stronger
LIMK-2	2.1 fold stronger
CaM-KI	2.1 fold stronger
JNK2	2.0 fold weaker
PRK	2.0 fold weaker
30 PTPzeta	4.6 fold weaker
PTP-SL	5.0 fold weaker
HSP86	4.1 fold weaker
GPIR-1	2.3 fold weaker

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Thus, one aspect of the present invention relates to a method for preventing and/or treating prion infections and/or diseases associated with said prion infections in an individual which comprises administering to the individual an amount of at least one compound of the general formula (I) and/or pharmaceutically acceptable salts

thereof effective to prevent and/or treat said prion infections and/or prion diseases. Most preferred is the administration of a compound according to claim 8.

5 It could be proven that inhibition of one target selected from FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 was effective to treat prion diseases. Therefore, another aspect of the invention relates to a method for preventing and/or treating prion infections and/or prion diseases in an individual comprising the step of administering a pharmaceutically effective amount of at least one compound according of the
10 general formula (I) and/or pharmaceutically acceptable salts thereof which inhibits at least partially the activity of one target selectef from FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

15 The nucleoside sequences of the genes coding for the human cellular protein kinase Abl and the protein kinase clk1 and their amino acid sequences are disclosed in form of a sequence listing shown below. The nucleoside and amino acid sequences for the kinase Abl (Accession Number: M14752) and for the kinase clk1 (Accession Numbers: XM002520, NM004071, L29222, L29219) were obtained from NCBI (National Library of Medicine: PubMed).

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The compounds of general formula (I) were identified as inhibitors of at least one target selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1 by the use of a method for detecting compounds useful for the prophylaxis and/or treatment of
25 prion infections and/or diseases. Said method comprises

- a) contacting a test compound with at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1; and
- 30 b) detecting the activity of said human cellular protein kinase, phosphatase or cellular signal transduction molecule.

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The activity of a human cellular protein kinase, phosphatase or cellular signal transduction molecule was preferably measured by means of an enzymatic assay.

As used herein, the term "inhibitor" refers to any compound capable of downregulating, decreasing, suppressing or otherwise regulating the amount and/or activity of at least one human cellular protein kinase, phosphatase or cellular

signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1. Generally, said inhibitors, including suicide inhibitors, may be proteins, oligo- and polypeptides, nucleic acids, genes, small chemical molecules, or other chemical moieties.

The present disclosure teaches for the first time the up- or downregulation of the above-mentioned human cellular protein kinases, phosphatases, or cellular signal transduction molecules specifically involved in prion infections and/or diseases. Thus, the present invention is also directed to a method for detecting prion infections and/or diseases in an individual comprising:

- a) providing a sample from said individual; and
- b) adding to said sample a pharmaceutically effective amount of at least one pharmaceutically active agent; and
- c) detecting activity in said sample of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.

As used herein the term "sample" refers to any sample that can be taken from a living animal or human for diagnostic purposes, especially said sample comprises blood, milk, saliva, sputum, excrement, urine, spinal cord liquid, liquor, lachrymal gland liquid, biopsies and all other samples that can be taken from a living animal or human for diagnostic purposes.

The term "individual" preferably refers to mammals, especially humans or ruminants. Ruminants are, for instance, muledeer, elk, cow, cattle, sheep, goat, deer, or buffalo. Minks are an example for mammals which do not belong to the species of ruminants.

As used herein the term "ruminants" refers to an animal, for instance, cattle, sheep, goat, deer, elk, or buffalo that has four separate stomach chambers, and is therefore able to digest a wide range of organic and plant foods. The term "ruminants" refers also to exotic ruminants, like captive nyala, gemsbok, Arabian oryx, eland, kudu, scimitar-horned oryx, ankole, or bison which are also accessible to develop spongiform encephalopathy.

A similar aspect of the present invention is directed to a method for detecting prion infections and/or prion diseases in cells, cell cultures and/or cell lysates comprising:

- a) providing said cells, cell cultures and/or cell lysates; and
- b) adding to said cells, cell cultures and/or cell lysates a pharmaceutically effective amount of at least one pharmaceutically active agent; and
- c) detecting activity in said sample of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.

Furthermore, it has been shown that the inhibition of at least one target selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1 has an effect on the production of prions. Therefore, another aspect of the invention relates to a method for regulating the production of prions in an individual or in cells comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which inhibits at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1, or which inhibits at least partially the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.

The inventive compounds according to general formula (I) are examples for the above-mentioned pharmaceutically active agent. Preferably the targets FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, and CDC 2 are used with said methods.

Another type of pharmaceutically active agents useful within the methods disclosed herein are monoclonal or polyclonal antibodies which bind to a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1. Thus, a further aspect of the present invention is related to said monoclonal or polyclonal antibodies which bind to a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1,

MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

Another embodiment of the present invention utilizes the scientific findings that some targets such as JNK2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 are downregulated during prion infection and that upregulation of the effected target by means of an activator leads to an alternative way of treating prion infections and diseases associated with prion infection.

Thus, a method was developed for regulating the production of prions either in an individual or in cells. Said methods comprise the step of administering an individual or the cells a pharmaceutically effective amount of at least one pharmaceutically active agent wherein said agent activates at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1, or wherein said agent at least partially activates or stimulates the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

Preferably the targets JNK2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 are used within the above-described methods.

Because of the fact that the organism may upregulate a given target such as FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, and CDC 2 in order to compete with the prion infection, it is also a reasonable approach to further support said upregulation by means of an activator. Therefore, the above-mentioned methods apply either to targets which are downregulated but also to targets which are upregulated.

The novel and partially known pyridylpyrimidine compounds of the general formula (I) represent a new class of pharmaceuticals highly useful for the prophylaxis and treatment of prion infections and prion diseases.

Thus, a further aspect of the present invention describes the use of a compound of the general formula (I) and/or pharmaceutically acceptable salts thereof for the

manufacture of a pharmaceutical formulation for prophylaxis and/or treatment of prion infections and/or diseases induced or caused by prion infection.

5 As used herein the Term "prion diseases" refers to transmissible spongiform encephalopathies. This group of neurologic diseases affects humans and many species of animals causing a "sponge-like" degeneration of brain tissue. Among other unique features, all of these diseases are associated with the accumulation of an abnormal form of the prion protein in nerve cells that eventually leads to the death of the host. While prion diseases can all be transmitted from one host to another, it remains contentious as to whether a virus-like infectious agent or the abnormal prion protein itself, the prion, causes the conversion of normal to abnormal protein.

15 Probably most mammalian species develop prion diseases. Specific examples for animals include:

- **Scrapie** sheep, goat
- **TME** (transmissible mink encephalopathy): mink
- **CWD** (chronic wasting disease): muledeer, deer, elk
- **BSE** (bovine spongiform encephalopathy): cows, cattles

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Humans are also susceptible to several prion diseases. Examples are:

- **CJD** Creutzfeld-Jacob Disease
- **GSS** Gerstmann-Sträussler-Scheinker syndrome
- **FFI** Fatal familial Insomnia
- 25 • **Kuru**
- **Alpers Syndrome**

30 The human prion diseases include kuru, sporadic Creutzfeldt-Jakob disease (sCJD), familial CJD (fCJD), iatrogenic CJD (iCJD), Gerstmann-Sträussler-Scheinker (GSS) disease, fatal familial insomnia (FFI), and, more recently, new variant CJD (nvCJD or vCJD). In addition to these human diseases, prion-related

diseases, have been recognized in several animal hosts. Scrapie is a naturally occurring disease of sheep and goats that causes ataxia, behavioral changes, and a severe pruritus that leads to scraping behavior, from which the disease was named. Additional prion diseases in animals include transmissible mink encephalopathy (TME), chronic wasting disease (CWD) of deer and elk, feline spongiform encephalopathy (FSE), and bovine spongiform encephalopathy (BSE), among others.

The transmissible nature of prion disease was first demonstrated experimentally in 1936 when Cuillé and Chelle transmitted scrapie to a healthy goat by the intraocular administration of scrapie-infected spinal cord. Thirty years later, sCJD was transmitted to chimpanzees. The pathologic feature common to all these diseases is a prominent vacuolation of the gray matter of the brain that produces a "sponge-like" appearance on light microscopy. This histopathologic appearance, coupled with the transmissible nature of these diseases, led to their collective designation as "transmissible spongiform encephalopathies" or TSEs.

The etiologic agent of the TSEs was proposed to be a "slow virus" to explain its transmissible nature and the prolonged incubation period observed during experimental transmission studies. Early experiments suggested that protein may be a critical component of the infectious agent. These studies established the basis for a new form of a transmissible pathogen, one that is composed ostensibly of only protein and lacks any replicative elements such as nucleic acid.

The term "prion" was coined to indicate an *infectious* agent with *proteinlike* properties. The unusual properties of the pathogen were demonstrated in early experiments in which conditions that degrade nucleic acids, such as exposure to ionizing and ultraviolet radiation, did not reduce the infectivity of scrapie fractions. On the other hand, treatments that degrade protein, such as prolonged exposure to proteases, correlated with a reduction in infectivity. A protein with relative resistance to protease digestion was found to be consistently present in the brains of animals and humans with TSE. Surprisingly, this protein was found to be one that is normally encoded by a chromosomal gene of the host.

Thus, the question raised, how a normally expressed protein could also be a transmissible pathogen? It was hypothesized and later demonstrated that PrP exists in two major isoforms: the nonpathogenic or cellular form, designated PrP^C, and the pathogenic or scrapie-inducing form, designated PrP^{Sc}. Both PrP^C and

PrP^{Sc} have the same amino acid sequence, yet they differ in their biochemical properties: PrP^C is soluble in nondenaturing detergents and completely degraded by proteases, whereas PrP^{Sc} is insoluble in nondenaturing detergents and shows a relative resistance to proteases. Structural studies of PrP^C and PrP^{Sc} indicate a difference in the conformation of the two isoforms: PrP^C is predominantly helical, whereas PrP^{Sc} contains at least 40% pleated sheet structure. Conversion to this sheet structure appears to be the fundamental event in prion disease. The ultimate mechanism of how cells die coincident with the generation of prions is still unclear. Simple accumulation of pathogenic protein may not be sufficient to explain disease, however, it may constitute a critical step in cellular dysfunction.

It was shown that the pyridylpyrimidine compounds of the general formula (I) are highly effective for the prophylaxis and/or treatment of prion infections and/or prion diseases selected from the group comprising Scrapie, TME, CWD, BSE, CJD, vCJD, GSS, FFI, Kuru, and Alpers Syndrome. Preferably, the pyridylpyrimidine derivatives are used for preventing and/or treating BSE, vCJD, or CJD.

The above-mentioned prion infections and/or diseases associated with prion infections can be treated using the inventive pyridylpyrimidine derivatives by targeting at least one of the human cellular protein kinases, phosphatases or cellular signal transduction molecules selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1. Thereby, the compounds according to general formula (I) act as inhibitors for at least one of the above-mentioned targets and especially as inhibitors for at least one enzyme selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, and CDC 2.

According to these findings a further aspect of the present invention is directed to a method for preventing and/or treating prion infections and/or prion diseases in an individual comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which inhibits at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1, or which inhibits at least partially the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.

Another aspect is related to a method for preventing and/or treating prion infections and/or prion diseases in cells or cell cultures comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which inhibits at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1, or which inhibits at least partially the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.

The inventive pyridylpyrimidine compounds of formula (I) are examples for the above-mentioned inhibitor. Said pyridylpyrimidine compounds and/or pharmaceutically acceptable salts thereof are administered in a dosage corresponding to an effective concentration in the range of 0.01 – 50 μ M, preferably in the range of 0.01 – 10 μ M, more preferably in the range of 0.01 – 1 μ M, and most preferably in the range of 0.01 – 0.1 μ M.

Because of the fact that the targets JNK2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 are downregulated in cells infected with prions, an upregulation of said targets represents another strategy in order to treat prion infections and diseases like CJD (nvCJD or vCJD) associated with prion infections. Said upregulation can be performed by activators.

An agent that is able to upregulate, increase, activate, or stimulate the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1, but especially of JNK2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 is named "activator".

Thus, another embodiment of the present invention describes a method for preventing and/or treating prion infections and/or diseases in an individual comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which activates at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal

transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1, or which activates or stimulates the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1. Preferably, said method is directed to the targets JNK2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

- 10 As used herein, the term "agent" or "pharmaceutically active agent" refers to any chemical compound capable of down- or upregulating, de- or increasing, suppressing, activation, stimulating or otherwise regulating the amount and/or activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1. Generally, said agents may be proteins, oligo- and polypeptides, nucleic acids, genes, aptamers, small chemical molecules, or other chemical moieties. An agent may be either an inhibitor or an activator and especially an inhibitor for the enzymes FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, and CDC 2 and an activator for the targets JNK2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

- One special kind of said pharmaceutically active agents are aptamers which function as regulators of the activity of a wide range of cellular molecules such as human cellular protein kinase and phosphatase. Aptamers are nucleic acid molecules selected in vitro to bind small molecules, peptides, or proteins with high affinity and specificity. Aptamers not only exhibit highly specific molecular recognition properties but are also able to modulate the function of their cognate targets in a highly specific manner by agonistic or antagonistic mechanisms. Most famous examples for aptamers are DNA aptamers or RNA aptamers.

- Further examples for pharmaceutically active agents are the pyridylpyrimidine compounds of the present invention and/or pharmaceutically acceptable salts thereof. Said compounds are administered in a dosage corresponding to an effective concentration in the range of 0.01 – 50 μ M, preferably in the range of 0.01 – 10 μ M, more preferably in the range of 0.01 – 1 μ M, and most preferably in the range of 0.01 – 0.1 μ M.

The compounds of general formula (I) can be administered in a daily dosage in the range of 25 mg to 1000 mg, preferably in a daily dosage of 400 mg to 600 mg, more preferably in a daily dosage of 500 mg, and most preferably in continuously increased daily dosages starting at a initial daily dosage of 400 mg and ending up in a daily dosage of 600 mg at the end of the treatment.

A question is how PrP^C does convert to PrP^{Sc}? Potential mechanisms that initiate conversion of PrP^C to PrP^{Sc} include a germ line mutation of the human prion protein gene (PRNP), a somatic mutation within a particular neuron, and spontaneous conversion of PrP^C to an aberrant conformation that is not refolded appropriately to its native structure. The prion protein gene (PRNP) is the single gene on the short arm of chromosome 20 in humans which encodes the normal cellular isoform of the prion protein. Regardless of the initiating event, once an "infectious unit" has been generated, PrP^{Sc} appears to act as a conformational template by which PrP^C is converted to a new molecule of PrP^{Sc} through protein-protein interaction of PrP^{Sc} and PrP^C. This concept is supported by several studies which show that mice with the normal PrP gene deleted (PrP knockout mice) do not develop prion disease after inoculation with scrapie. Furthermore, transgenic (Tg) mice that express a chimeric PrP gene made of human and mouse segments develop protease-resistant chimeric mouse-human PrP^{Sc} in their brains when inoculated with brain extracts from humans with prion disease. These findings clearly illustrate that prions do not self-replicate but instead convert nonpathogenic PrP^C to pathogenic PrP^{Sc}.

In its sporadic or nonfamilial form, CJD is the most common of the human prion diseases. Confusion and forgetfulness which progress rapidly to severe cortical dementia in combination with ataxia, myoclonus, and an abnormal electroencephalogram (EEG) represents the "classic tetrad" of CJD. However, a host of other neurologic signs and symptoms, including diffuse or focal weakness, painful neuropathy, choreiform movements, hallucinations, cortical blindness, primary language disturbance, supranuclear ophthalmoplegia, and alien hand syndrome, among others, have been observed. As the disease progresses from the early stage, ataxia commonly limits the patient's mobility.

Familial CJD (fCJD) includes those cases with a dominantly inherited mutation of the PRNP gene, in which the pathologic features of spongiform change occur in the absence of GSS-type plaques. Although, familial cases of CJD tend to have a clinical and pathologic phenotype similar to that of sCJD.

The original description of a patient with the onset of ataxia and dysarthria followed by variable degrees of pyramidal and extrapyramidal symptoms and late developing dementia defines the classic presentation of **GSS**. The duration of said disease ranges from 2 to 10 years. Death usually results from secondary infection, often from aspiration pneumonia because of impaired swallowing. The presence of plaque deposits regionally or diffusely throughout the cortex that are immunoreactive to anti-human PrP antibodies is the hallmark of this form of prion disease.

FFI is a genetic disorder which manifests itself by many symptoms due to the degeneration of a certain part of the brain, the thalamus. The affected area of the brain is the area responsible for sleep, the thalamus. The thalamus is the center which communications from the brain to the body and the body to the brain pass through for proper directions to where a signal should be received. When sleep takes place, it is thought that the thalamus becomes less efficient at this signal transfer function allowing for the vegetative state of sleep to come over an individual. Consequently, the symptoms of fatal familial insomnia are directly related to the malfunction of the responsibilities of the thalamus, namely sleep.

There are four stages of the disease before an individual's life ends. The first stage is progressive insomnia, the characteristic feature of fatal familial insomnia. By now, there is no cure for this illness.

The term "familial" means: affecting several members of the same family, usually as a result of an underlying genetic mutation.

The occurrence of **vCJD** is sobering because it appears to represent a situation in which the prion has "jumped" species, in this case from cow to human. Because the pathologic features and clinical presentation of vCJD differ significantly from those of sCJD, it is considered a new "strain" of human prion disease. The same "protein signature" was observed following experimental transmission of BSE to several animal hosts, supporting the idea that vCJD results from the infection of humans with BSE. vCJD occurs primarily in younger individuals (average age 27) with a somewhat protracted course of approximately 16 months. The brain shows diffuse vacuolation and the presence of distinctive dense core PrP-containing plaques surrounded by a halo of spongiform change.

Kuru is the condition which first brought prion diseases to prominence in the 1950s. The disease was found in geographically isolated tribes in New Guinea. It was established that ingesting brain tissue of dead relatives for religious reasons was likely to be the route of transmission.

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Alpers Syndrome is the name given to prion diseases in infants.

Scrapie is the accepted, albeit somewhat colloquial, name for the naturally occurring transmissible spongiform encephalopathy of sheep and goats found worldwide. Scrapie also infects laboratory mice and hamsters making it one of the most important sources of new scientific information about this group of disorders. Scrapie was the first example of this type of disease to be noticed and has been known about for many hundreds of years. There are two possible methods of transmission in sheep: a) Infection of pasture with placental tissue carrying the agent followed by ingestion, or b) direct sheep-lamb transmission.

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CWD is a fatal neurodegenerative disease of deer and elk, now known to be a transmissible spongiform encephalopathy. To date, affected animals have been found exclusively in the United States.

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BSE

Bovine spongiform encephalopathy or "mad cow disease" appears to have originated from scrapie that has been recognized in Europe since the mid-18th century. It has since spread to most sheep-breeding countries and is widespread in the United Kingdom, where until 1988 the rendered carcasses of livestock (including sheep) were fed to ruminants and other animals as a protein-rich nutritional supplement.

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During rendering, carcasses from which all consumable parts had been removed were milled and then decomposed in large vats by boiling at atmospheric or higher pressures, producing an aqueous slurry of protein under a layer of fat (tallow). After the fat was removed, the slurry was desiccated into a meat and bone meal product that was packaged by the animal food industry and distributed to owners of livestock and other captive animals (e.g., zoo and laboratory animals, breeding species, pets).

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A further aspect is related to a method for regulating the expression of at least one human cellular protein kinase, phosphatase or cellular signal transduction

molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 in an individual comprising the step of administering the individual a pharmaceutically effective amount of at least one pharmaceutically active agent wherein said agent
5 inhibits at least partially the transcription of DNA or the translation of RNA.

And a still further aspect of the present invention relates to a method for regulating the expression of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1,
10 Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 in the cells, the method comprising the step of administering the cells a pharmaceutically effective amount of at least one pharmaceutically active agent wherein said agent inhibits at least partially the transcription of DNA or the translation of RNA.

15 As used herein, the term "regulating expression and/or activity" generally refers to any process that functions to control or modulate the quantity or activity (functionality) of a cellular component. Static regulation maintains expression and/or activity at some given level. Upregulation refers to a relative increase in
20 expression and/or activity. Accordingly downregulation refers to a relative decrease in expression and/or activity. Downregulation is synonymous with inhibition of a given cellular component's activity.

The transcription of DNA and the translation of RNA can be inhibited by
25 oligonucleotides or oligonucleotide derivatives. Thus, the present invention discloses oligonucleotides and derivatives of oligonucleotides which may be used in the above-mentioned methods. The oligonucleotide and/or its derivatives bind to the DNA and/or RNA encoding a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from the group comprising FGF-R1,
30 Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 and suppress the transcription of DNA or translation of RNA.

As described above, said prion infection and/or disease associated with said prion infection is selected from the group comprising Scrapie, TME, CWD, BSE, vCJD, CJD, GSS, FFI, Kuru, and Alpers Syndrome. Preferably, the method is used for
35 prophylaxis and/or treatment of BSE, vCJD, or CJD. The above disclosed methods are preferably applied to CJD, vCJD, and BSE, more preferably applied to vCJD and BSE, and most preferably applied to BSE.

Some methods of the present invention identify compounds useful for prophylaxis and/or treatment of prion infections and/or diseases by screening a test compound, or a library of test compounds, for its ability to inhibit at least one of the above-mentioned human cellular protein kinases, phosphatases, or cellular signal transduction molecules, identified herein as characteristically up- or downregulated during prion production or growth inside a cell or individual. A variety of assay protocols and detection techniques are well known in the art and easily adapted for this purpose by a skilled practitioner. Such methods include, but are not limited to, high throughput assays (e.g., microarray technology, phage display technology), and *in vitro* and *in vivo* cellular and tissue assays.

Thus, a solid support is disclosed in the present invention useful for screening compounds useful for the prophylaxis and/or treatment of prion infections and/or diseases in an individual, the solid support comprising at least one immobilized oligonucleotide, wherein said oligonucleotide encodes one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

A further aspect of the present invention is related to a solid support useful for screening compounds useful for the prophylaxis and/or treatment of prion infections and/or diseases in an individual, the solid support comprising at least one immobilized human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

In another embodiment, a component of the above-mentioned methods comprises peptide fragments of one or more of the above-identified human cellular protein kinases, phosphatases or cellular signal transduction molecules immobilized on a solid support. Once again the most preferred solid support embodiment would contain polymers of sufficient quality and quantity to detect all of the above-mentioned human cellular protein kinases, phosphatase and cellular signal transduction molecules (e.g., a nucleic acid or a peptide microarray). A variety of supports and constructions of the same for the methods disclosed herein are well known in the art and easily adapted for this purpose by a skilled practitioner (cf.,

for example: Marschall, 1999 "Do-it-yourself gene watching" Science 286, 444-447; Service 2000 "Protein arrays step out of DNA's shadow" Science 289, 1673).

It is preferred that mRNA is measured as an indication of expression. Methods for assaying for mRNA include, but are not limited to, Northern blots, slot blots, dot blots, and hybridization to an ordered array of oligonucleotides. Nucleic acid probes useful for assay of a sample are preferably of sufficient length to specifically hybridize only to appropriate, complementary transcripts. Typically the oligonucleotide probes will be at least 10 to 25 nucleotides in length. In some cases longer probes of at least 30 to 50 nucleotides will be desirable.

The cDNA oligonucleotides immobilized on said membrane filter which are used for detecting the up- or downregulation of the above-mentioned human cellular protein kinases, phosphatases, and cellular signal transduction molecules by hybridization to the radioactively labeled cDNA probes have the nucleotide sequences listed in table 1.

Table 1: Nucleotide sequences of cDNA-arrays

Cellular kinase, phosphatase, or signal transduction molecule	Sequence of immobilized DNA on arrays (in relation to the respective Acc No)
FGF-R1	41 bp – 2619bp (X52833)
Tkt (EC 2.7.1.112)	1 bp – 3096bp (X74764)
Abl	2153 bp – 3765 bp (M14752)
clk1	156 bp -1610 bp (L29219)
MKK7	77 bp – 1323 bp (AF013588)
CDC2	77 bp – 1050 bp (X05360)
CaMKI	145 bp – 1452 bp (L41816)
JNK2	507 bp – 1782 bp (L31951)
LIMK-2	963 bp – 2047 bp (D45906)
PRK	n.a bp – 1862 bp (U56998)
PTP zeta (EC 3.1.3.48)	148 bp – 7604 bp (X54135)
PTP-SL	862 bp – 1902 bp (NM_002849)
HSP86	n.a bp – n.a bp (X07270)
GPIR-1	n.a bp – n.a bp (n.a)

Tkt has been assigned to the EC Number: 2.7.1.112

PTP zeta has been assigned to the EC Number : 3.1.3.48

The nucleoside sequences of the genes coding for the human cellular protein kinases, phosphatases, or cellular signal transduction molecules listed in Table 1 together with the amino acid sequences and the enzyme commission numbers (E.C. numbers) of said enzymes can be obtained from NCBI (National Library of Medicine: PubMed; Web address: www.ncbi.nlm.nih.gov/entrez).

The polypeptide product of gene expression may be assayed to determine the amount of expression as well. Methods for assaying for a protein include, but are not limited to, western blot, immuno-precipitation, radioimmuno assay, and peptide immobilization in an ordered array. It is understood, however, that any method for specifically and quantitatively measuring a specific protein or mRNA product can be used.

A variety of supports upon which nucleic acids or peptides can be immobilized are known in the art, for example filters, or polyvinyl chloride dishes. Any solid surface to which oligonucleotides or peptides can be bound, either directly or indirectly, either covalently or non-covalently, can be used. A preferred solid support is a microarray membrane filter or a "biochip". These contain particular polymer probes in predetermined locations on the array. Each predetermined location may contain more than one molecule of the probe, but each molecule within the predetermined location has an identical sequence.

The present invention incorporates by reference in their entirety techniques well known in the field of molecular biology. These techniques include, but are not limited to, techniques described in the following publications:

Ausubel, F.M. et al. eds., "Short Protocols In Molecular Biology" 4th Ed. 1999, John Wiley & Sons, NY (ISBN 0-471-32938-X);

Old, R.W. & S.B. Primrose "Principles of Gene Manipulation: An Introduction To Genetic Engineering" 3rd Ed. 1985, Blackwell Scientific Publications, Boston. Studies in Microbiology: V.2, 409 pp. (ISBN 0-632-01318-4);

Mayer, R.J. & J.H. Walker eds. "Immunochemical Methods In Cell and Molecular Biology" 1987, Academic Press, London. 325 pp. (ISBN 0-12480-855-7);

Winnacker, E.L. "From Genes To Clones: Introduction To Gene Technology" 1987 VCH Publishers, NY. (translated by Horst Ibelgauf) 634 pp. (ISBN 0-89573-614-4).

As described above, a microarray platform technology was developed consisting of more than 1100 signal transduction cDNAs immobilized on a solid support. Thus, another aspect of the present invention is directed to a solid support useful for detecting prion infections and/or diseases in an individual, the solid support comprising an immobilized oligonucleotide, wherein said oligonucleotide is capable of detecting activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

The present invention discloses also for the first time a solid support useful for detecting prion infections and/or diseases in cells, the solid support comprising an immobilized oligonucleotide, wherein said oligonucleotide is capable of detecting activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

The present invention further incorporates by reference in their entirety techniques well known in the field of microarray construction and analysis. These techniques include, but are not limited to, techniques described in the following patents and patent applications describing array of biopolymeric compounds and methods for their fabrication:

U.S. Pat. Nos. 5,807,522; 6,087,102; WO 93/17126; WO 95/11995; WO 95/35505; EP 742 287; and EP 799 897.

Techniques also include, but are not limited to, techniques described in the following patents and patent application describing methods of using arrays in various applications:

U.S. Pat. Nos. 5,994,076; 6,033,860; 6,040,138; 6,040,140; WO 95/21265; WO 96/31622; WO 97/10365; WO 97/27317; EP 373 203; and EP 785 280

Still a further aspect of the present invention is directed to pharmaceutical compositions comprising at least one pharmaceutically active agent together with a pharmaceutically acceptable carrier, excipient or diluents. Examples for

pharmaceutically active agents are the above-mentioned inventive compounds according to formula (I), or other small chemical molecules, antibodies, aptamers, oligo- and polynucleotides, genes and other biological components capable of regulating the activity of at least one target selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1, or which are effective to treat prion infections and diseases associated with prion infection. Said prion infections and diseases are preferably Scrapie, TME, CWD, BSE, vCJD, CJD, GSS, FFI, Kuru, and Alpers Syndrome.

Thus, the pharmaceutical compositions according to the present invention may comprise an inhibitor, such as the inventive pyridylpyrimidine compounds or an activator such as aptamers for at least one target selected from FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1. It is also possible to have a combination of inhibitors or activators as active ingredients in one single pharmaceutical composition. Furthermore, suitable are also combinations of at least one inhibitor and at least one activator for different targets within a single pharmaceutical composition. For example, a pharmaceutical composition could comprise compound 12 as an inhibitor for, for instance, the target Abl, and an activator such as an aptamer for, for instance, the human cellular protein kinase JNK2.

Said pharmaceutical compositions are useful for the prophylaxis and/or treatment of an individual afflicted with prions comprising at least one agent capable of inhibiting and/or activating at least partially the activity, the expression, and/or the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

The pyridylpyrimidine compounds of the present invention are basic and form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for such acid addition salt formation are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, citric acid, oxalic acid, malonic acid, salicylic acid, p-aminosalicylic acid, malic acid, fumaric acid, succinic acid, ascorbic acid, maleic acid, sulfonic acid, phosphonic acid, perchloric acid, nitric acid, formic acid, propionic acid, gluconic acid, lactic acid, tartaric acid, hydroxymaleic acid, pyruvic acid, phenylacetic acid, benzoic acid, p-aminobenzoic

acid, p-hydroxybenzoic acid, methanesulfonic acid, ethanesulfonic acid, nitrous acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, p-toluenesulfonic acid, naphthylsulfonic acid, sulfanilic acid, camphorsulfonic acid, china acid, mandelic acid, o-methylmandelic acid, hydrogen-benzenesulfonic acid, picric acid, adipic acid, d-o-tolytartaric acid, tartronic acid, α -toluic acid, (o, m, p)-toluic acid, naphthylamine sulfonic acid, and other mineral or carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner.

It is also possible to obtain acid addition salts with amino acids like methionine, tryptophane, lysine or arginine, especially with pyridylpyrimidine compounds of the general formula (I) carrying a carboxylic acid residue.

Depending upon the substituents on the inventive pyridylpyrimidine compounds, one may be able to form salts with bases, too. Thus, for example, if there are carboxylic acid substituents in the molecule, salts may be formed with inorganic as well as organic bases such as, for example, NaOH, KOH, NH_4OH , tetraalkylammonium hydroxide, and the like.

The compounds of the general formula (I) can also be administered in form of their pharmaceutically active salts optionally using substantially nontoxic pharmaceutically acceptable carriers, excipients or diluents. The medications of the present invention are prepared in a conventional solid or liquid carrier or diluents and a conventional pharmaceutically-made adjuvant at suitable dosage level in a known way. The preferred preparations are in administratable form which is suitable for oral application. These administratable forms, for example, include pills, tablets, film tablets, coated tablets, capsules, powders and deposits.

The preferred administratable forms are tablets, film tablets, coated tablets, gelatin capsules, and opaque capsules. Each pharmaceutical composition contains at least one compound of the general formula (I), preferably compound 53 and/or pharmaceutically acceptable salts thereof in an amount of 50 mg to 150 mg, preferably 80 mg to 120 mg, and most preferably in an amount of 100 mg per formulation.

Furthermore, the subject of the present invention also includes pharmaceutical preparations for parenteral, including dermal, intradermal, intragastrical,

intracutaneous, intravasal, intravenous, intramuscular, intraperitoneal, intranasal, intravaginal, intrabuccal, percutaneous, rectal, subcutaneous, sublingual, topical or transdermal application, which in addition to typical vehicles and diluents contain a pyridylpyrimidine compound of the general formula (I) and/or a pharmaceutically acceptable salt thereof as active ingredient.

Within the disclosed methods the pharmaceutical compositions of the present invention, containing pyridylpyrimidine derivatives of the general formula (I) as active ingredients, will typically be administered in admixture with suitable carrier materials selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral nontoxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition.

Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants, there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate. Some of the terms noted above, namely disintegrants, diluents, lubricants, binders and the like, are discussed in more detail below.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e. antihistaminic activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components

and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

5 Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injections or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

10 Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier such as inert compressed gas, e.g. nitrogen.

15 For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein by stirring or similar mixing. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidifies.

20 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

25 The inventive pyridylpyrimidine compounds of the present invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

30 The term capsule refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

35 Tablet means compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of

mixtures or granulations obtained by wet granulation, dry granulation or by compaction well known to a person skilled in the art.

5 Oral gels refers to the active ingredients dispersed or solubilized in a hydrophilic semi-solid matrix.

Powders for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

10 Suitable diluents are substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol, starches derived from wheat, corn rice and potato, and celluloses such as microcrystalline cellulose. The amount of diluents in the composition can range from about 5 to about 95% by weight of the total
15 composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight.

The term disintegrants refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants
20 include starches, "cold water soluble" modified starches such as sodium carboxymethyl starch, natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar, cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose, microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose, alginates such as
25 alginic acid and sodium alginate, clays such as bentonites, and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 5 to about 10% by weight.

30 Binders characterize substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluents or bulking agent. Suitable binders include sugars such as sucrose, starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and
35 tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The

amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

5 Lubricant refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high
10 melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and D,L-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from
15 about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glidants are materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidants include silicon
20 dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents are excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes
25 adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

As used herein, a "pharmaceutically effective amount" of an inhibitor and/or an
30 activator is an amount effective to achieve the desired physiological result, either in cells treated *in vitro* or in a subject treated *in vivo*. Specifically, a pharmaceutically effective amount is an amount sufficient to inhibit and or activate, for some period of time, one or more of the clinically defined pathological processes associated with the prion infection. The effective amount may vary
35 depending on the specific inhibitor and/or activator selected, and is also dependent on a variety of factors and conditions related to the subject to be treated and the severity of the infection. For example, if an inhibitor and/or activator is to be administered *in vivo*, factors such as the age, weight and health

of the patient as well as dose response curves and toxicity data obtained in pre-clinical animal work would be among those considered. If the inhibitor and/or activator is to be contacted with the cells *in vitro*, one would also design a variety of pre-clinical *in vitro* studies to assess such parameters as uptake, half-life, dose, toxicity, etc. The determination of a pharmaceutically effective amount for a given pharmaceutically active agent is well within the ability of those skilled in the art.

It is also apparent to a person skilled in the art that detection includes any method known in the art useful to indicate the presence, absence, or amount of a detection target. Such methods may include, but are not limited to, any molecular or cellular techniques, used singularly or in combination, including, but not limited to: hybridization and/or binding techniques, including blotting techniques and immunoassays; labeling techniques (chemiluminescent, colorimetric, fluorescent, radioisotopic); spectroscopic techniques; separations technology, including precipitations, electrophoresis, chromatography, centrifugation, ultrafiltration, cell sorting; and enzymatic manipulations (e.g., digestion).

It should be stressed that all above-mentioned features, aspects, and details of the present invention discussed and described in connection with infections and infectious diseases, equally apply to neurodegenerative diseases, like Alzheimer.

It is readily apparent to those skilled in the art that other suitable modifications and adaptations of the compositions and methods of the invention described herein are evident and may be made without departing from the scope of the invention or the embodiments disclosed herein. Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included for purposes of illustration only and are not intended to be limiting of the invention.

Description of figures

Fig. 1 shows 6 selected pyridylpyrimidine derivatives which are suitable inhibitors for prion diseases, namely compounds 4, 5, 37, 52, 84, and 88;

Fig. 2 shows the compound 4-(4-Methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide, also known as GleevecTM;

Fig. 3 shows selected compounds that have been identified as potent inhibitors in a prion propagation assay at a concentration of 5 μ m.

Examples

Materials and methods

5

1. Generation of cDNA-arrays on membranes

In order to manufacture cDNAs-arrays on membranes, the following strategy was pursued: cDNAs encoding parts of or full length proteins of interest – in the following referred to as “target cDNAs” – were cloned into the plasmid Bluescript II KS⁺ (Stratagene, USA). Large scale purifications of these plasmids were performed according to standard techniques and 200 µl aliquots (1 µg/µl plasmid concentration) were transferred into appropriate 96well plates. Plates were closed with sealing tape and chilled on ice for 5 minutes after incubation for 10 minutes at 95°C. 10 µl of 0.6 N NaOH were added and the mix was stored for 20 minutes at room temperature before addition of 10 µl 2.5 M Tris-HCl pH 7.1 and 20 µl 40x SSC (3 M NaCl, 300 mM Sodium Citrate, pH 7.0). Target cDNAs were spotted onto Nylon or Nitrocellulose membranes using a BioGrid (BioRobotics, UK) equipped with a 0.7 mm pintool. In this way, between 200 ng and 350 ng of plasmids encoding target cDNAs were transferred onto the membranes and crosslinked to the membranes by ultraviolet light (1.2×10^5 µJ/cm²). The arrays were stored for use in subsequent experiments at room temperature.

25

2. Generation of cells

PrP^{Sc}- and PrP^C-transfected mouse neuronal cells (N2A) were cultured in MEM (Minimum Essential Medium, Life Technologies) supplemented with 10% fetal calf serum at 37°C and 5% CO₂ to obtain $\sim 6 \times 10^6$ cells per tissue culture flask.

30

3. Lysis of cells, isolation of total RNA and purification of polyA⁺ RNA

After incubation of the cells with the virus for the respective time-points, cells were washed twice with phosphate buffered saline (PBS) and then trypsinized. Subsequently, cells were removed from the culture dish by resuspension with PBS. Afterwards, cells were sedimented and directly lysed in Tri reagent by repetitive pipetting using in 1ml of Tri reagent (Molecular Research Centre, Inc., USA) per 1×10^6 cells.

The lysates were stored at room temperature for 5 minutes and then centrifuged at 12000xg for 15 minutes at 4°C. The supernatant was mixed with 0,1 ml of 1-bromo-3-chloropropane per 1 ml of Tri reagent and vigorously shaken. The suspension was stored for 5 minutes at room temperature and then centrifuged at 12000xg for 15 minutes at 4°C.

The colourless upper phase was transferred into new tubes, mixed with 5 µl of poly-acryl-carrier (Molecular Research Centre, Inc., USA) and with 0.5 ml of isopropanol per 1 ml of Tri reagent and vigorously shaken. The samples were stored at room temperature for 5 minutes and then centrifuged at 12000xg for 8 minutes at 4°C. The supernatant was removed and the RNA pellet washed twice with 1 ml of 75% ethanol. The pellet was dried and resuspended for 10 minutes at 55°C in 50 µl of RNase-free buffer (5 mM Tris-HCl pH 7.5). The integrity of the isolated RNA was determined by agarose/formaldehyde gel electrophoresis and the RNA was finally stored at -70°C for use in subsequent experiments.

4. Preparation of radioactively labelled cDNA probes from RNA

In order to obtain radioactively labelled cDNA probes total RNA was transcribed into a cDNA-probe in the presence of radioactively labelled dATP. 12 µl bidistilled DEPC (Diethylpyrocarbonate) treated H₂O containing 0.5 µg of primer TXN (5'-TTT TTT TTT TTT TTT TXN-3' with T → dTTP; N → dATP, dCTP, dGTP or dTTP; X → dATP, dCTP or dGTP) and total RNA (1 to 10 µg) were shaken between 5 and 15' at 60°C and then incubated on ice for 2 minutes. After centrifugation (30 seconds, 10000xg) 7 µl of a mix consisting of 100 µCi dATP-P³³ (Amersham, UK) which were dried under vacuum previously and resuspended in 4 µl first strand buffer (Life Technologies, USA), 2 µl 0.1M DTT (Dithiothreitol) and 1 µl labelling solution (4 mM dCTP, dGTP, dTTP each and 80 µM dATP final concentration) were added. Following the addition of 1 µl Superscript II reverse transcriptase (Life Technologies, USA) the reaction was incubated for 10 minutes at room temperature and then for 60 minutes at 38°C. Subsequently, the reaction was vigorously shaken for 30 minutes at 68°C after adding 5 µl 0.5 M EDTA and 25 µl 0.6M NaOH.

Unincorporated nucleotides were removed from the labelling reaction using ProbeQuant G-50 columns (Amersham, UK). The column was vigorously shaken and centrifuged for 1 minute at 735xg in an appropriate reaction tube after bottom closure and lid were removed. The column was placed into a new reaction tube,

the probe was applied onto the centre of the column material and the column was centrifuged for 2 minutes at 735xg. The flow-trough was transferred into new reaction tubes and filled up to a volume of 100 µl with bidistilled H₂O. The probe was precipitated by centrifugation for 15 minutes at 12000xg after 4 µl 5M NaCl, 1
5 µl poly-acryl-carrier (Molecular Research Centre, Inc., USA) and 250 µl ethanol were added. The supernatant was discarded and the pellet was dried at 50°C for 5 minutes before starting with the hybridisation.

5. Hybridisation of radioactively labelled cDNA-probes to cDNA-arrays

10

The pellet was resuspended in 10 µl C₀T DNA (1 µg/µl, Roche Diagnostics, Germany), 10 µl yeast tRNA (1µg/µl Sigma, USA) and 10 µl polyA (1 µg/µl, Roche Diagnostics, Germany) and incubated at 55°C for 5 minutes. Herring sperm DNA was added to a final concentration of 100 µg/ml and the volume was filled up to
15 100 µl with 5 µl 10% SDS (Sodiumdodecylsulfat), 25 µl 20x SSPE (3M Sodium chloride, 0,2 M Sodium dihydrogen phosphate monohydrate, 0,02 M Ethylenedinitrilo tetraacetic acid, disodium salt dihydrate; pH 7,4) and bidistilled H₂O. The mix was put on 95°C for 5 minutes, centrifuged for 30 seconds at 10000xg and vigorously shaken for 60 minutes at 65°C. A 1 µl aliquot of the
20 probe was used to measure the incorporation of radioactive dATP with a scintillation counter. Probes with at least a total of 20x10⁶ cpm were used.

The arrays were prehybridised for at least 3 hours at 42°C in hybridisation solution in a roller bottle oven. After prehybridization the radioactively labelled probe was
25 added into the hybridisation solution and hybridisation was continued for 20 to 40 hours.

The probe was discarded and replaced with wash solution A (2xSSC). The arrays were washed twice in wash solution A at room temperature in the roller
30 oven. Afterwards, wash solution A was replaced by wash solution B (2x SSC, 0.5% SDS) preheated to 65°C and arrays were washed twice for 30 minutes at 65°C. Then, wash solution B was replaced by wash solution C (0.5x SSC, 0.5% SDS) preheated to 65°C and arrays were washed twice for 30 minutes at 65°C. The moist arrays were wrapped in airtight bags and exposed for 8 to 72 hours on
35 erased phosphoimager screens (Fujifilm, Japan).

6. Analysis of cDNA-arrays

The exposed phosphoimager screens were scanned with a resolution of 100 μ and 16bits per pixel using a BAS-1800 (Fujifilm, Japan). Files were imported into the computer program ArrayVision (Imaging Research, Canada). Using the program's features, the hybridization signals of each target cDNA were converted into numbers. The strength of the hybridization signals reflected the quantity of RNA molecules present in the probe. Differentially expressed genes were selected according to the ratio of their signal strength after normalization to the overall intensity of the arrays.

7. Cell culture and expression of 3F4-tagged PrP (3F4-ScN2a)

The mouse neuroblastoma cell line 3F4-ScN2a represents a stably transfected clone of ScN2a cells (PrP^{Sc} infected N2a cells) which overexpress 3F4-epitope-tagged murine PrP. Residues 109 and 112 of murine PrP were replaced by methionine to introduce the epitope for reactivity with the monoclonal anti-PrP antibody 3F4. Cells were maintained in Dulbecco's modified Eagle's (DMEM) or Opti-MEM medium containing 10 % fetal calf serum, antibiotics and glutamin. For generation of stable transfectants we used the vector pcDNA3.1/Zeo (Invitrogen; Leek, The Netherlands). Lipofection of cells with recombinant plasmids was done using standard procedures and recombinant clones were selected by addition of 300 μ g Zeocin/ml medium.

8. Treatment of cells with inhibitors

All tested compounds were solubilized in DMSO (dimethylsulfoxide), and prepared as 10 mM stock solutions. The drugs were applied to the cells described above for three days in final concentrations between 5 and 20 μ M.

9. Immunoblot and proteinase K (PK) analysis

Confluent cell cultures were lysed in cold lysis buffer (10 mM Tris-HCl, pH 7.5; 100 mM NaCl; 10 mM EDTA; 0.5 % Triton X-100; 0.5 % DOC) (EDTA: ethylene diamine tetraacetate; Triton X-100: t-octylphenoxypolyethoxyethanol; DOC: deoxycholic acid). Postnuclear lysates were split between those with and without proteinase K digestion. Samples without proteinase K digestion were supplemented with proteinase inhibitors (5 mM PMSF, 0.5 mM Pefabloc, and aprotinin) (PMSF: phenylmethylsulfonyl fluoride) and directly precipitated with ethanol. Samples for proteinase K digestion were incubated with 20 μ g/ml proteinase K for 30 min at 37°C; digestion was stopped with proteinase inhibitors,

and samples were ethanol precipitated. After centrifuging for 30 min at 3,500 rpm the pellets were redissolved in TNE buffer (10 mM Tris-HCl pH7.5, 100 mM NaCl, 1mM EDTA) and gel loading buffer was then added. After boiling for 5 min an aliquot was analyzed on 12.5 % PAGE. For Western blot analysis, the proteins were electrotransferred to PVDF membranes (polyvinylidendifluoride). The membrane was blocked with 5 % non-fat dry milk in TBST (0.05 % Tween 20, 100 mM NaCl, 10 mM Tris-HCl, pH 7.8) (Tween 20: polyoxyethylenesorbitan monolaurate; Tris-HCl: Tris-(hydroxymethyl)-aminomethane-hydrochloride), incubated overnight with the primary antibody at 4°C and stained using the enhanced chemiluminescence blotting kit from Amersham Corporation. Specific immuno-staining of the PrP^c and PrP^{Sc} forms were obtained with the prion protein specific antibody 3F4 (Signet Pathologies, U.S.A.).

10. Results

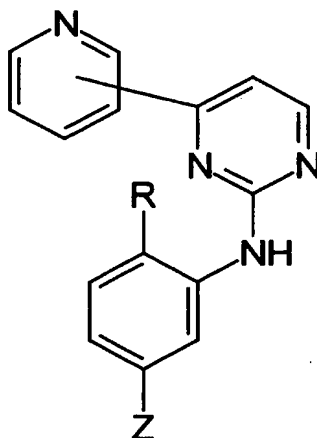
Determination of the amount of the pathogenic form of the prion protein PrP^{Sc} upon treatment of prion infected cells with different types of small molecule protein kinase inhibitors resulted in the identification of a compound class of pyridylpyrimidine derivatives exemplified by the compound 4-(4-Methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide (compound 53) and compounds 4, 5, and 37.

These compounds significantly reduced the amount of PrP^{Sc} in prion infected cells in a concentration range between 5 and 20 µM (final concentration). As shown in Fig. 3 the selected compounds 4, 5, 37, and 53 inhibit almost completely the activity of prion propagation within said concentration range.

The compounds did not show any toxic effects on the cells in these concentrations. Therefore these molecules described herein serve as potential inhibitors for the medical intervention of prion diseases such as transmissible spongiform encephalitis (TSE) infections which include Bovine spongiform encephalitis (BSE) or the new variant of Creutzfeld Jakob disease (vCJK).

Claims

1. Compounds having the general formula (I):



5

wherein:

R represents hydrogen or methyl;

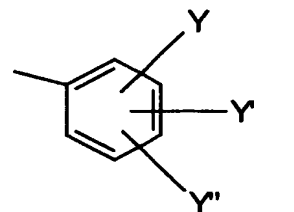
10

Y, Y', Y'' are independently of each other -H, -F, -Cl, -Br, -I, -CH₂F, -CH₂Cl, -CH₂Br, -CH₂I, -OH, -OCH₃, -CH₃, -CN, -OCF₃, 4-methylpiperazin-1-yl-methyl, -C(CH₃)=N-NH-C(NH)-NH₂;

Z represents -NO₂, -NH₂, -NH-CO-X, -NH-CS-X, -NH-CO-NH-X, -NH-SO₂-X;

X represents thiophenyl, cyclohexyl, isoquinolinyl, naphthyl, quinolinyl,

cyclopentyl, pyridinyl, naphthyridinyl, or

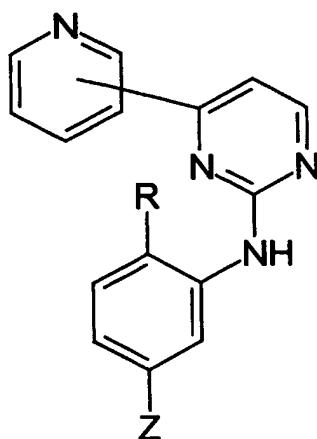


15

and pharmaceutically acceptable salts thereof.

20

2. Use of a compound having the general formula (I):



5 wherein:

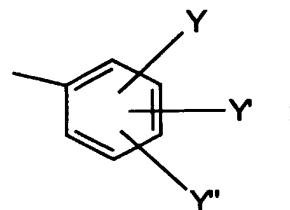
R represents hydrogen or methyl;

Y, Y', Y'' are independently of each other -H, -F, -Cl, -Br, -I, -CH₂F, -CH₂Cl, -CH₂Br, -CH₂I, -OH, -OCH₃, -CH₃, -CN, -OCF₃, 4-methylpiperazin-1-yl-methyl, -C(CH₃)=N-NH-C(NH)-NH₂;

10 Z represents -NO₂, -NH₂, -NH-CO-X, -NH-CS-X, -NH-CO-NH-X, -NH-SO₂-X;

X represents thiophenyl, cyclohexyl, isoquinolinyl, naphthyl, quinolinyl,

cyclopentyl, pyridinyl, naphthyridinyl, or

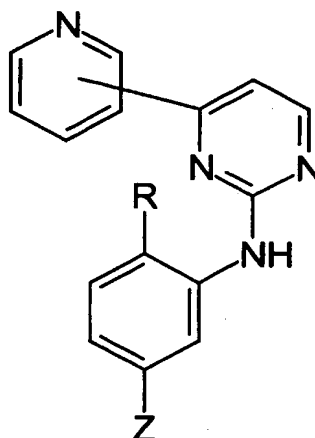


and pharmaceutically acceptable salts thereof as pharmaceutically active agents.

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3. Use of a compound having the general formula (I):



5. wherein:

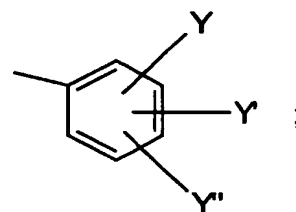
R represents hydrogen or methyl;

Y, Y', Y'' are independently of each other -H, -F, -Cl, -Br, -I, -CH₂F, -CH₂Cl, -CH₂Br, -CH₂I, -OH, -OCH₃, -CH₃, -CN, -OCF₃, 4-methylpiperazin-1-yl-methyl, -C(CH₃)=N-NH-C(NH)-NH₂;

10 Z represents -NO₂, -NH₂, -NH-CO-X, -NH-CS-X, -NH-CO-NH-X, -NH-SO₂-X;

X represents thiophenyl, cyclohexyl, isoquinolinyl, naphthyl, quinolinyl,

cyclopentyl, pyridinyl, naphthyridinyl, or



and pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of infectious diseases or neurodegenerative diseases.

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4. Use of a compound according to claim 2 or 3 for the prophylaxis and/or treatment of prion infections and/or diseases induced by prion infection.

5. Use of a compound according to any one of claims 2 - 4 wherein R represents hydrogen.

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6. Use of a compound according to any one of claims 2 - 5 wherein Z represents -NH-CO-X or -NH-SO₂-X.

7. Use of a compound according to any one of claims 2 – 6 wherein Y, Y', Y'' are independently of each other –H, –F, –Cl, –CH₂F, –CH₂Cl, –OH, –OCH₃, –CH₃, –CN, –OCF₃, 4-methylpiperazin-1-yl-methyl.
- 5 8. Use of a compound according to claim 2 or 3 wherein the compound is selected from the group comprising:
- (3-Nitrophenyl)-(4-pyridin-3-yl-pyrimidin-2-yl)-amine;
(3-Aminophenyl)-(4-pyridin-3-yl-pyrimidin-2-yl)-amine;
10 (5-Amino-2-methylphenyl)-(4-pyridin-3-yl-pyrimidin-2-yl)-amine;
4-Chloromethyl-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
4-Chloromethyl-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
4-(4-Methylpiperazin-1-ylmethyl)-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-
15 phenyl]-benzamide;
Thiophene-3-carboxylic acid [4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-amide;
4-Chloro-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
4-Chloro-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
20 3,4,5-Trimethoxy-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
4-Cyano-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
4-Methoxy-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
25 4-Chloro-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;
Thiophene-3-carboxylic acid [3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
3,5-Dimethoxy-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
30 3,4,5-Trimethoxy-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
4-Cyano-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
4-Methoxy-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-
35 benzamide;
4-Chloro-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;

- Thiophene-3-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 3,5-Dimethoxy-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 5 4-Trifluoromethoxy-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 10 Cyclohexanecarboxylic acid [3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Isoquinoline-5-sulfonic acid [4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- Isoquinoline-5-sulfonic acid [3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 15 (5-Nitro-2-methylphenyl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine;
- (5-Amino-2-methylphenyl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine;
- 3,4,5-Trimethoxy-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 4-Cyano-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 20 (3-Aminophenyl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine;
- 4-Chloro-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 25 4-Cyano-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 4-Chloro-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;
- 30 4-Methoxy-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 4-Chloro-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Cyclohexanecarboxylic acid [3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 35 3,5-Dimethoxy-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- (5-Amino-2-methylphenyl)-(4-pyridin-4-yl-pyrimidin-2-yl)-amine;

- Thiophene-3-carboxylic acid [3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 4-Chloro-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;
- 5 4-Chloro-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- (3-Aminophenyl)-(4-pyridin-4-yl-pyrimidin-2-yl)-amine;
- (3-Nitrophenyl)-(4-pyridin-4-yl-pyrimidin-2-yl)-amine;
- 4-Trifluoromethoxy-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 10 Isoquinoline-5-sulfonic acid [3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 4-Methoxy-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 4-Cyano-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 3,4,5-Trimethoxy-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-
- 15 benzamide;
- 3,5-Dimethoxy-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 3,4,5-Trimethoxy-*N*-[4-methyl-3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 20 4-(4-Methylpiperazin-1-ylmethyl)-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 4-Methyl-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;
- 4-Methoxy-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-
- 25 benzamide;
- 3,5-Dimethoxy-*N*-[4-methyl-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- Naphthalene-2-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;
- 30 *N*-[3-(4-Pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 4-Chloro-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 4-Methoxy-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
- 4-Chloro-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzenesulfonamide;
- 35 Thiophene-2-carboxylic acid 3-(4-pyridin-2-yl-pyrimidin-2-yl-amino)-phenyl]-amide;
- Naphthalene-2-sulfonic-acid [3-(4-pyridin-2-yl-pyrimidin-2-yl-amino)-phenyl]-amide;

Isoquinoline-5-sulfonic-acid [3-(4-pyridin-2-yl-pyrimidin-2-yl-amino)-phenyl]-amide;

Cyclopentanecarboxylic acid 3-(4-pyridin-2-yl-pyrimidin-2-yl-amino)-phenyl]-amide;

5 Naphthalene-2-carboxylic acid [3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-amide;

4-Cyano-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

3,5-Dimethoxy-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

4-Bromo-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

10 4-Methyl-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

4-Fluoro-*N*-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-

benzenesulfonamide;

3,5-Dichloro-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

N-[3-(4-Pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

15 4-Chloromethyl-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

4-Methyl-*N*-3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-

benzenesulfonamide;

4-(4-Methylpiperazin-1-ylmethyl)-*N*-[3-(4-pyridin-2-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

20 Naphthalene-2-carboxylic acid [3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-amide;

2-Methoxy-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

2-Methoxy-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

25 4-Methyl-*N*-[3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

4-Methyl-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

N-[4-Methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;

30 1-(3,5-Diacetyl-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-urea;

1-{3,5-Bis-(amidinohydrazone)-phenyl}-3-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-urea;

N-[4-Methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-nicotinamide;

N-[3-(4-Pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-nicotinamide;

35 [1,8]Naphthyridine-2-carboxylic acid [3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;

[1,8]Naphthyridine-2-carbothioic acid [3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-amide;

2-Methoxy-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
4-Trifluoromethoxy-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-
benzamide;
4-Methyl-*N*-[3-(4-pyridin-4-yl-pyrimidin-2-ylamino)-phenyl]-benzamide;
and/or a pharmaceutically acceptable salt of these compounds.

9. Use according to claim 8 wherein the compound is 4-(4-Methylpiperazin-1-ylmethyl)-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide.

10. Use of a compound recited in any one of claims 2 – 9 and/or pharmaceutically acceptable salts thereof for the manufacture of a pharmaceutical composition for prophylaxis and/or treatment of prion infections and/or diseases induced by prion infection and/or neurodegenerative diseases.

11. Use according to claim 4 or 10 wherein said prion infection and/or disease is selected from the group comprising Scrapie, TME, CWD, BSE, CJD, vCJD, GSS, FFI, Kuru, and Alpers Syndrome.

12. Use according to claim 11 wherein said prion infection is BSE, vCJD, or CJD.

13. Use of a compound recited in any one of claims 2 – 9 as an inhibitor for at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.

14. Use of a compound according to any one of claims 2 to 13 wherein the compound of the general formula (I) and/or pharmaceutically acceptable salts thereof is administered in a dosage corresponding to an effective concentration in the range of 0.01 – 50 μ M.

15. Pharmaceutical composition comprising at least one compound recited in any one of claims 2 – 9 as an active ingredient, together with one or more pharmaceutically acceptable carrier(s), excipient(s) or diluents.

16. Method for preventing and/or treating infections and/or diseases in an individual which comprises administering to the individual an amount of at least one compound recited in claims 2 – 9 and/or pharmaceutically acceptable salts thereof effective to prevent and/or treat said infections and/or diseases.
17. Method for preventing and/or treating prion infections and/or prion diseases induced by prion infections in an individual which comprises administering to the individual an amount of at least one compound recited in any one of claims 3 to 8 and/or pharmaceutically acceptable salts thereof effective to prevent and/or treat said prion infection and/or disease.
18. Method for preventing and/or treating prion infections and/or prion diseases induced by prion infections in an individual which comprises administering to the individual an amount of at least one compound recited in claim 8 and/or pharmaceutically acceptable salts thereof effective to prevent and/or treat said prion infection and/or disease.
19. Method for detecting prion infections and/or prion diseases in an individual comprising:
- a) providing a sample from said individual;
 - b) adding to said sample a pharmaceutically effective amount of at least one pharmaceutically active agent; and
 - c) detecting activity in said sample of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.
20. Method according to claim 19 wherein said sample comprises blood, milk, saliva, sputum, excrement, urine, spinal cord liquid, liquor, lachrymal gland liquid, biopsies and all other samples that can be taken from a living animal or human for diagnostic purposes.
21. Method for detecting prion infections and/or prion diseases in cells, cell cultures and/or cell lysates comprising:
- a) providing said cells, cell cultures and/or cell lysates;
 - b) adding to said cells, cell cultures and/or cell lysates a pharmaceutically effective amount of at least one pharmaceutically active agent; and

- c) detecting activity in said sample of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.

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22. Method for preventing and/or treating prion infections and/or prion diseases in an individual comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which inhibits at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1, or which inhibits at least partially the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.

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23. Method for preventing and/or treating prion infections and/or prion diseases in cell or cell cultures comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which inhibits at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1, or which inhibits at least partially the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.

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24. Method for regulating the production of prions in an individual comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which inhibits at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1, or which inhibits at least partially the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt,

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Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.

- 5 25. Method for regulating the production of prions in cells comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which inhibits at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, 10 HSP86, GPIR-1, or which inhibits at least partially the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1.
- 15 26. A monoclonal or polyclonal antibody that binds to a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.
- 20 27. Method according to any one of claims 19 – 25, wherein the agent is a monoclonal or polyclonal antibody which binds to a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, 25 JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.
- 30 28. Method according to any one of claims 19 – 25, wherein the agent is at least one compound of the general formula (I) and/or pharmaceutically acceptable salts thereof.
- 35 29. Method according to any one of claims 16 – 25, wherein the agent is 4-(4-Methylpiperazin-1-ylmethyl)-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-yl-amino)-phenyl]-benzamide and/or pharmaceutically acceptable salts thereof.
30. Method according to claim 28 wherein the compound of the general formula (I) and/or pharmaceutically acceptable salts thereof is administered in a dosage corresponding to an effective concentration in the range of 0.01 – 50 μ M.

31. Method for detecting compounds useful for the prophylaxis and/or treatment of prion infections and/or diseases comprising:
- 5 a) contacting a test compound with at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1; and
- 10 b) detecting the activity of said human cellular protein kinase, phosphatase or cellular signal transduction molecule.
32. Method for preventing and/or treating prion infections and/or diseases in an individual comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which activates at least
- 15 partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1, or which activates or stimulates the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the
- 20 group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.
33. Method for regulating the production of prions in an individual comprising the step of administering an individual a pharmaceutically effective amount of at
- 25 least one pharmaceutically active agent wherein said agent activates at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1, or wherein said
- 30 agent at least partially activates or stimulates the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.
- 35 34. Method for regulating the production of prions in cells comprising the step of administering the cells a pharmaceutically effective amount of at least one pharmaceutically active agent wherein said agent activates at least partially

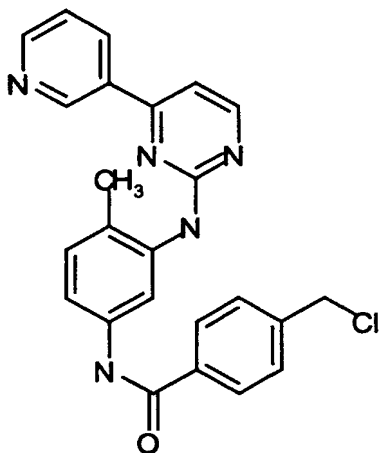
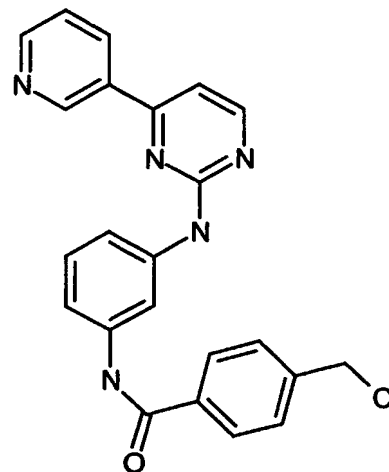
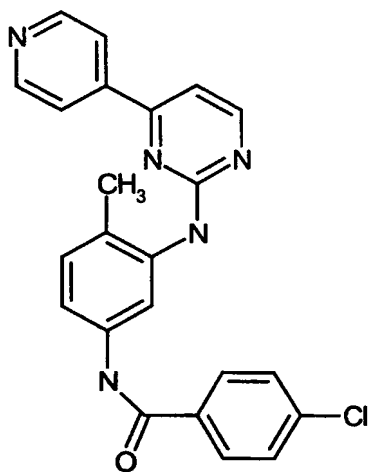
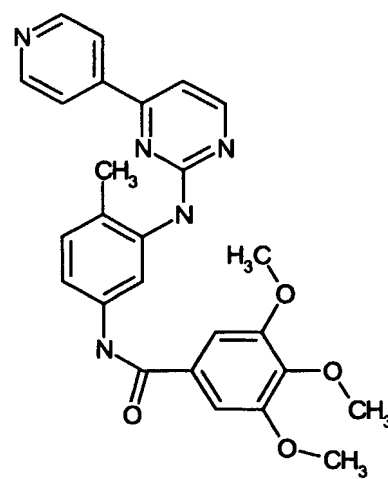
the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1, or wherein said agent at least partially activates or stimulates the production of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 in the cells.

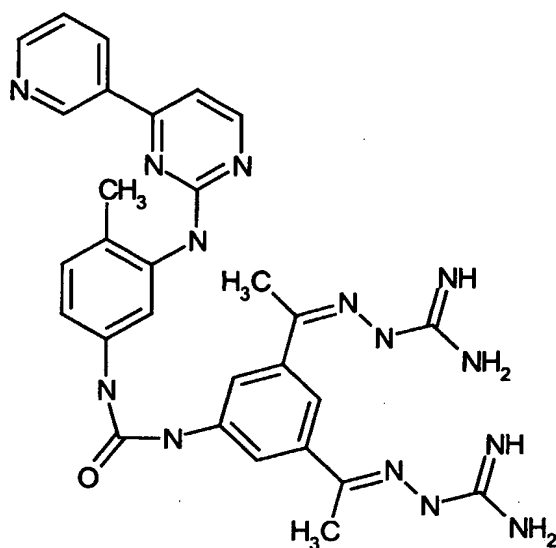
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- 10 35. Method for regulating the expression of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 in an individual comprising the step of administering the individual a
- 15 pharmaceutically effective amount of at least one pharmaceutically active agent wherein said agent inhibits at least partially the transcription of DNA or the translation of RNA.
- 20 36. Method for regulating the expression of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 in the cells comprising the step of administering the cells a pharmaceutically effective amount of at least one pharmaceutically active agent wherein said agent
- 25 inhibits at least partially the transcription of DNA or the translation of RNA.
- 30 37. Oligonucleotide that binds to the DNA or RNA encoding a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.
- 35 38. Method according to claim 22, 23, 24, 25, 35 or 36 wherein the agent is a oligonucleotide which binds to the DNA and/or RNA encoding a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

39. Method according to claims 16, 17, 18, 19, 22, 24, 32, 33, or 35 wherein said individual is a human or ruminant.
- 5 40. Method according to any one of claims 17, 18, 19, 21, 22, 23, 31, or 32 wherein said prion infection and/or prion disease is selected from the group comprising Scrapie, TME, CWD, BSE, vCJD, CJD, GSS, FFI, Kuru, and Alpers Syndrome.
- 10 41. Method according to claim 40 wherein said prion infection and/or prion disease is BSE, vCJD, or CJD.
- 15 42. A solid support useful for detecting prion infections and/or diseases in an individual, the solid support comprising an immobilized oligonucleotide, wherein said oligonucleotide is capable of detecting activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.
- 20 43. A solid support useful for detecting prion infections and/or diseases in cells, the solid support comprising an immobilized oligonucleotide, wherein said oligonucleotide is capable of detecting activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.
- 25 44. A solid support useful for screening compounds useful for the prophylaxis and/or treatment of prion infections and/or diseases in an individual, the solid support comprising at least one immobilized oligonucleotide, wherein said oligonucleotide encodes one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.
- 30 45. A solid support useful for screening compounds useful for the prophylaxis and/or treatment of prion infections and/or diseases in an individual, the solid support comprising at least one immobilized human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the

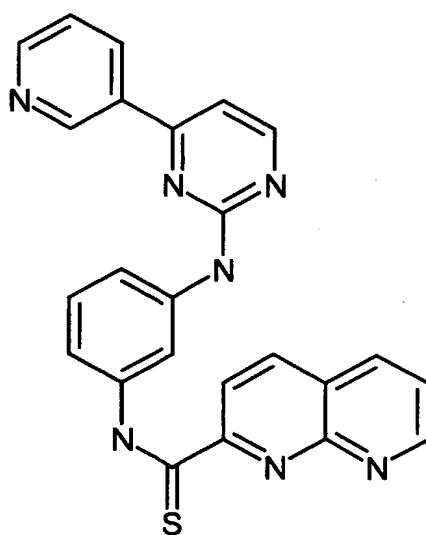
group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.

- 5 46. Composition useful for the prophylaxis and/or treatment of an individual afflicted with prions comprising at least one agent capable of inhibiting at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.
- 10 47. Composition useful for the prophylaxis and/or treatment of an individual afflicted with prions comprising at least one agent capable of activating or stimulating at least partially the activity of at least one human cellular protein kinase, phosphatase or cellular signal transduction molecule selected from the group comprising FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1.
- 15 48. Composition according claim 46 or 47, wherein the agent is at least one compound of the general formula (I) and/or pharmaceutically acceptable salts thereof.
- 20

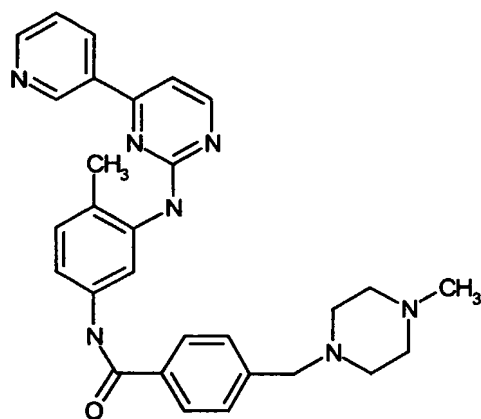
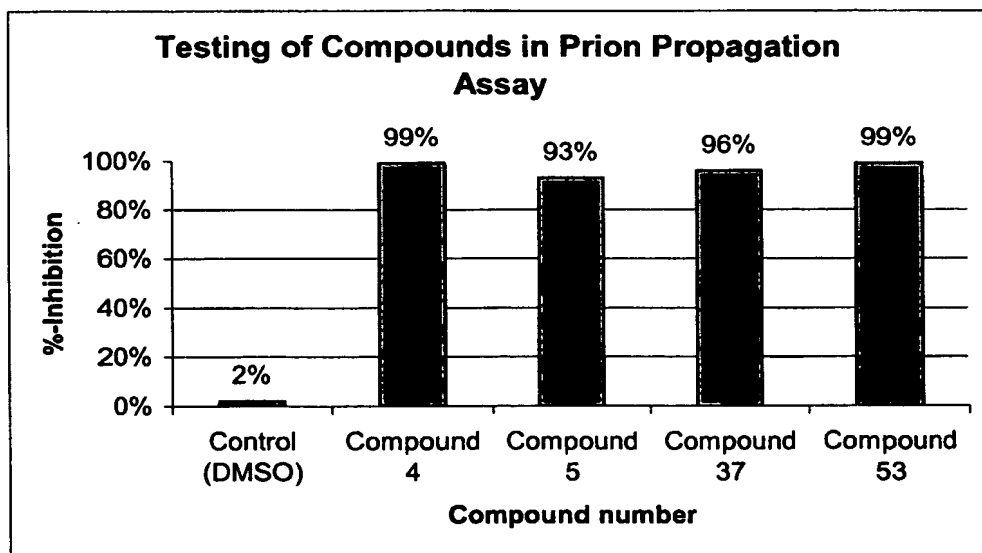
Fig. 1**Compound 4****Compound 5****Compound 37****Compound 52**



Compound 84



Compound 88

Fig. 2**Compound 53 (Gleevec™)****Fig. 3**

SEQUENCE LISTING

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targets for diagnosis and treatment of prion diseases

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 20 gcggcaggtc accgtggccc ctgcctcggg cctccccac aaggaagaag cctggaaagg 2880
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 25 ccaggaggct gccggggagg cagtcttggg cgcaaagaca aaagccacga gtctggttga 3180
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 30 tccagagcgg gccagcggcg ccacaccaa gggcggtggtc ttggacagca ccgaggcgct 3480
 gtgcctcgcc atctctggga actccgagca gatggccagc cacagcgagc tgctggaggc 3540
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 ctgcccggcg tcagcaggca gtggtccggc ggccactcag gacttcagca agctcctcag 3720
 35 ttcggtgaag gaaatcagt acatagtga gaggtagcag cagtcagggg tcaggtgtca 3780
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<210> 4

<211> 1130

<212> PRT

<213> Homo sapiens

5

<220>

<223> Description of Sequence: N/A

<400> 4

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 Leu Ser Ser Ser Ser Ser Cys Tyr Leu Glu Glu Ala Leu Gln Arg Pro
 20 25 30
 Val Ala Ser Asp Phe Glu Pro Gln Gly Leu Ser Glu Ala Ala Arg Trp
 15 35 40 45
 Asn Ser Lys Glu Asn Leu Leu Ala Gly Pro Ser Glu Asn Asp Pro Asn
 50 55 60
 Leu Phe Val Ala Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn Thr Leu
 65 70 75 80
 20 Ser Ile Thr Lys Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn His Asn
 85 90 95
 Gly Glu Trp Cys Glu Ala Gln Thr Lys Asn Gly Gln Gly Trp Val Pro
 100 105 110
 Ser Asn Tyr Ile Thr Pro Val Asn Ser Leu Glu Lys His Ser Trp Tyr
 25 115 120 125
 His Gly Pro Val Ser Arg Asn Ala Ala Glu Tyr Pro Leu Ser Ser Gly
 130 135 140
 Ile Asn Gly Ser Phe Leu Val Arg Glu Ser Glu Ser Ser Pro Ser Gln
 145 150 155 160
 30 Arg Ser Ile Ser Leu Arg Tyr Glu Gly Arg Val Tyr His Tyr Arg Ile
 165 170 175
 Asn Thr Ala Ser Asp Gly Lys Leu Tyr Val Ser Ser Glu Ser Arg Phe
 180 185 190
 Asn Thr Leu Ala Glu Leu Val His His His Ser Thr Val Ala Asp Gly
 35 195 200 205
 Leu Ile Thr Thr Leu His Tyr Pro Ala Pro Lys Arg Asn Lys Pro Thr
 210 215 220
 Val Tyr Gly Val Ser Pro Asn Tyr Asp Lys Trp Glu Met Glu Arg Thr

	225					230						235				240
	Asp	Ile	Thr	Met	Lys	His	Lys	Leu	Gly	Gly	Gly	Gln	Tyr	Gly	Glu	Val
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	Tyr	Glu	Gly	Val	Trp	Lys	Lys	Tyr	Ser	Leu	Thr	Val	Ala	Val	Lys	Thr
5				260					265					270		
	Leu	Lys	Glu	Asp	Thr	Met	Glu	Val	Glu	Glu	Phe	Leu	Lys	Glu	Ala	Ala
				275					280					285		
	Val	Met	Lys	Glu	Ile	Lys	His	Pro	Asn	Leu	Val	Gln	Leu	Leu	Gly	Val
				290				295				300				
10	Cys	Thr	Arg	Glu	Pro	Pro	Phe	Tyr	Ile	Ile	Thr	Glu	Phe	Met	Thr	Tyr
	305						310				315					320
	Gly	Asn	Leu	Leu	Asp	Tyr	Leu	Arg	Glu	Cys	Asn	Arg	Gln	Glu	Val	Asn
							325				330				335	
	Ala	Val	Val	Leu	Leu	Tyr	Met	Ala	Thr	Gln	Ile	Ser	Ser	Ala	Met	Glu
15				340						345				350		
	Tyr	Leu	Glu	Lys	Lys	Asn	Phe	Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn
				355					360					365		
	Cys	Leu	Val	Gly	Glu	Asn	His	Leu	Val	Lys	Val	Ala	Asp	Phe	Gly	Leu
				370				375				380				
20	Ser	Arg	Leu	Met	Thr	Gly	Asp	Thr	Tyr	Thr	Ala	His	Ala	Gly	Ala	Lys
	385						390				395					400
	Phe	Pro	Ile	Lys	Trp	Thr	Ala	Pro	Glu	Ser	Leu	Ala	Tyr	Asn	Lys	Phe
							405				410				415	
	Ser	Ile	Lys	Ser	Asp	Val	Trp	Ala	Phe	Gly	Val	Leu	Leu	Trp	Glu	Ile
25				420						425				430		
	Ala	Thr	Tyr	Gly	Met	Ser	Pro	Tyr	Pro	Gly	Ile	Asp	Arg	Ser	Gln	Val
				435					440				445			
	Tyr	Glu	Leu	Leu	Glu	Lys	Asp	Tyr	Arg	Met	Lys	Arg	Pro	Glu	Gly	Cys
				450				455				460				
30	Pro	Glu	Lys	Val	Tyr	Glu	Leu	Met	Arg	Ala	Cys	Trp	Gln	Trp	Asn	Pro
	465						470				475					480
	Ser	Asp	Arg	Pro	Ser	Phe	Ala	Glu	Ile	His	Gln	Ala	Phe	Glu	Thr	Met
							485				490				495	
	Phe	Gln	Glu	Ser	Ser	Ile	Ser	Asp	Glu	Val	Glu	Lys	Glu	Leu	Gly	Lys
35				500						505				510		
	Gln	Gly	Val	Arg	Gly	Ala	Val	Thr	Thr	Leu	Leu	Gln	Ala	Pro	Glu	Leu
				515					520				525			
	Pro	Thr	Lys	Thr	Arg	Thr	Ser	Arg	Arg	Ala	Ala	Glu	His	Arg	Asp	Thr

	530					535					540					
	Thr	Asp	Val	Pro	Glu	Met	Pro	His	Ser	Lys	Gly	Gln	Gly	Glu	Ser	Asp
	545					550					555					560
5	Pro	Leu	Asp	His	Glu	Pro	Ala	Val	Ser	Pro	Leu	Leu	Pro	Arg	Lys	Glu
					565					570					575	
	Arg	Gly	Pro	Pro	Glu	Gly	Gly	Leu	Asn	Glu	Asp	Glu	Arg	Leu	Leu	Pro
					580				585					590		
	Lys	Asp	Lys	Lys	Thr	Asn	Leu	Phe	Ser	Ala	Leu	Ile	Lys	Lys	Lys	Lys
					595			600					605			
10	Lys	Thr	Ala	Pro	Thr	Pro	Pro	Lys	Arg	Ser	Ser	Ser	Phe	Arg	Glu	Met
	610						615					620				
	Asp	Gly	Gln	Pro	Glu	Arg	Arg	Gly	Ala	Gly	Glu	Glu	Glu	Gly	Arg	Asp
	625					630					635					640
15	Ile	Ser	Asn	Gly	Ala	Leu	Ala	Phe	Thr	Pro	Leu	Asp	Thr	Ala	Asp	Pro
					645					650					655	
	Ala	Lys	Ser	Pro	Lys	Pro	Ser	Asn	Gly	Ala	Gly	Val	Pro	Asn	Gly	Ala
					660				665					670		
	Leu	Arg	Glu	Ser	Gly	Gly	Ser	Gly	Phe	Arg	Ser	Pro	His	Leu	Trp	Lys
					675				680				685			
20	Lys	Ser	Ser	Thr	Leu	Thr	Ser	Ser	Arg	Leu	Ala	Thr	Gly	Glu	Glu	Glu
	690						695					700				
	Gly	Gly	Gly	Ser	Ser	Ser	Lys	Arg	Phe	Leu	Arg	Ser	Cys	Ser	Val	Ser
	705					710					715					720
25	Cys	Val	Pro	His	Gly	Ala	Lys	Asp	Thr	Glu	Trp	Arg	Ser	Val	Thr	Leu
					725					730					735	
	Pro	Arg	Asp	Leu	Gln	Ser	Thr	Gly	Arg	Gln	Phe	Asp	Ser	Ser	Thr	Phe
					740				745				750			
	Gly	Gly	His	Lys	Ser	Glu	Lys	Pro	Ala	Leu	Pro	Arg	Lys	Arg	Ala	Gly
					755				760				765			
30	Glu	Asn	Arg	Ser	Asp	Gln	Val	Thr	Arg	Gly	Thr	Val	Thr	Pro	Pro	Pro
	770						775					780				
	Arg	Leu	Val	Lys	Lys	Asn	Glu	Glu	Ala	Ala	Asp	Glu	Val	Phe	Lys	Asp
	785					790					795					800
35	Ile	Met	Glu	Ser	Ser	Pro	Gly	Ser	Ser	Pro	Pro	Asn	Leu	Thr	Pro	Lys
					805					810					815	
	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ala	Pro	Ala	Ser	Gly	Leu	Pro	His
					820				825				830			
	Lys	Glu	Glu	Ala	Trp	Lys	Gly	Ser	Ala	Leu	Gly	Thr	Pro	Ala	Ala	Ala

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	Thr Ser Lys Gly Pro Ala Glu Glu Ser Arg Val Arg Arg His Lys His		
5	865	870	875 880
	Ser Ser Glu Ser Pro Gly Arg Asp Lys Gly Lys Leu Ser Lys Leu Lys		
	885	890	895
	Pro Ala Pro Pro Pro Pro Pro Ala Ala Ser Ala Gly Lys Ala Gly Gly		
	900	905	910
10	Lys Pro Ser Gln Arg Pro Gly Gln Glu Ala Ala Gly Glu Ala Val Leu		
	915	920	925
	Gly Ala Lys Thr Lys Ala Thr Ser Leu Val Asp Ala Val Asn Ser Asp		
	930	935	940
	Ala Ala Lys Pro Ser Gln Pro Ala Glu Gly Leu Lys Lys Pro Val Leu		
15	945	950	955 960
	Pro Ala Thr Pro Lys Pro His Pro Ala Lys Pro Ser Gly Thr Pro Ile		
	965	970	975
	Ser Pro Ala Pro Val Pro Leu Ser Thr Leu Pro Ser Ala Ser Ser Ala		
	980	985	990
20	Leu Ala Gly Asp Gln Pro Ser Ser Thr Ala Phe Ile Pro Leu Ile Ser		
	995	1000	1005
	Thr Arg Val Ser Leu Arg Lys Thr Arg Gln Pro Pro Glu Arg Ala Ser		
	1010	1015	1020
	Gly Ala Ile Thr Lys Gly Val Val Leu Asp Ser Thr Glu Ala Leu Cys		
25	1025	1030	1035 1040
	Leu Ala Ile Ser Gly Asn Ser Glu Gln Met Ala Ser His Ser Ala Val		
	1045	1050	1055
	Leu Glu Ala Gly Lys Asn Leu Tyr Thr Phe Cys Val Ser Tyr Val Asp		
	1060	1065	1070
30	Ser Ile Gln Gln Met Arg Asn Lys Phe Ala Phe Arg Glu Ala Ile Asn		
	1075	1080	1085
	Lys Leu Glu Asn Asn Leu Arg Glu Leu Gln Ile Cys Pro Ala Ser Ala		
	1090	1095	1100
	Gly Ser Gly Pro Ala Ala Thr Gln Asp Phe Ser Lys Leu Leu Ser Ser		
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	Val Lys Glu Ile Ser Asp Ile Val Gln Arg		
	1125	1130	

<210> 5

<211> 1461

5 <212> DNA

<213> Homo sapiens

<220> MKK7

<223> Description of Sequence: N/A

10

<400> 5

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gcaggagaac cgggaggccc ggcggaggat cgacctcaac ctggatatca gccccagcg 180
15 gcccaggccc accctgcagc tcccgtggc caacgatggg ggcagccgct cgccatcctc 240
agagagctcc ccgcagcacc ccacgcccc cgccggccc cgccacatgc tggggctccc 300
gtcaaccctg ttcacacccc gcagcatgga gagcattgag attgaccaga agctgcagga 360
gatcatgaag cagacgggct acctgaccat cggggggccag cgctaccagg cagaaatcaa 420
cgacctggag aacttgggcg agatgggcag cggcacctgc ggccagggtg ggaagatgcg 480
20 cttccggaag accggccacg tcattgccgt taagcaaatg cggcgctccg ggaacaagga 540
ggagaacaag cgcatcctca tggacctgga tgtggtgctg aagagccacg actgccccta 600
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tctgggcaag atgacagtgg cgattgtgaa ggcgctgtac tacctgaagg agaagcacgg 780
25 tgtcatccac cgcgacgtca agccctccaa catcctgctg gacgagcggg gccagatcaa 840
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35 cctccccact tggccacca gctgcctgcc aggggagacc tgggacctgg acggccacct 1440
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1461

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<210> 6

<211> 419

<212> PRT

<213> Homo sapiens

5

<220>

<223> Description of Sequence: N/A

<400> 6

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 Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Arg Ile Asp Leu Asn Leu
 20 25 30
 Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala
 15 35 40 45
 Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro Gln His
 50 55 60
 Pro Thr Pro Pro Ala Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr
 65 70 75 80
 20 Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu
 85 90 95
 Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg
 100 105 110
 Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser
 25 115 120 125
 Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His
 130 135 140
 Val Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn
 145 150 155 160
 30 Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys
 165 170 175
 Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val
 180 185 190
 Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys
 35 195 200 205
 Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val
 210 215 220
 Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile

225 230 235 240
 His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln
 245 250 255
 Ile Lys Phe Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp Ser Lys
 5 260 265 270
 Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro Glu Arg
 275 280 285
 Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg Ala Asp
 290 295 300
 10 Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly Gln Phe
 305 310 315 320
 Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys Val Leu
 325 330 335
 Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser Gly Asp
 15 340 345 350
 Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg Lys Arg
 355 360 365
 Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys Arg Tyr Glu
 370 375 380
 20 Thr Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met Ala Lys
 385 390 395 400
 Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln Pro His Leu Pro
 405 410 415
 Phe Phe Arg
 25

 <210> 7
 <211> 1050
 30 <212> DNA
 <213> Homo sapiens

 <220> CDC2
 <223> Description of Sequence: N/A
 35

 <400> 7
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ctaactatgg aagattatac caaaatagag aaaattggag aagggtaccta tggagttgtg 180
 tataagggtta gacacaaaac tacaggtcaa gtggttagcca tgaaaaaat cagactagaa 240
 agtgaagagg aaggggttcc tagtactgca attcgggaaa tttctctatt aaaggaactt 300
 cgtcatccaa atatagtcag tcttcaggat gtgcttatgc aggattccag gttatatctc 360
 5 atctttgagt ttctttccat ggatctgaag aaatacttgg attctatccc tcctggtcag 420
 tacatggatt cttcacttgt taagagttat ttataccaaa tcctacaggg gattgtgttt 480
 tgtcactcta gaagagttct tcacagagac ttaaaacctc aaaatctctt gattgatgac 540
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 gtatatacac atgaggtagt aacactctgg tacagatctc cagaagtatt gctgggggtca 660
 10 gctcgttact caactccagt tgacatttgg agtataggca ccatatttgc tgaactagca 720
 actaagaaac cacttttcca tggggattca gaaattgatc aactcttcag gattttcaga 780
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 aatggcttgg atttgctctc gaaaatgtta atctatgatc cagccaaacg aatttctggc 960
 15 aaaatggcac tgaatcatcc atattttaat gatttggaca atcagattaa gaagatgtag 1020
 ctttctgaca aaaagtttcc atatgttatg 1050

<210> 8

20 <211> 297

<212> PRT

<213> Homo sapiens

<220>

25 <223> Description of Sequence: N/A

<400> 8

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 20 25 30
 Lys Lys Ile Arg Leu Glu Ser Glu Glu Gly Val Pro Ser Thr Ala
 35 40 45
 Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu Arg His Pro Asn Ile Val
 35 50 55 60
 Ser Leu Gln Asp Val Leu Met Gln Asp Ser Arg Leu Tyr Leu Ile Phe
 65 70 75 80
 Glu Phe Leu Ser Met Asp Leu Lys Lys Tyr Leu Asp Ser Ile Pro Pro

85 90 95
 Gly Gln Tyr Met Asp Ser Ser Leu Val Lys Ser Tyr Leu Tyr Gln Ile
 100 105 110
 Leu Gln Gly Ile Val Phe Cys His Ser Arg Arg Val Leu His Arg Asp
 5 115 120 125
 Leu Lys Pro Gln Asn Leu Leu Ile Asp Asp Lys Gly Thr Ile Lys Leu
 130 135 140
 Ala Asp Phe Gly Leu Ala Arg Ala Phe Gly Ile Pro Ile Arg Val Tyr
 145 150 155 160
 10 Thr His Glu Val Val Thr Leu Trp Tyr Arg Ser Pro Glu Val Leu Leu
 165 170 175
 Gly Ser Ala Arg Tyr Ser Thr Pro Val Asp Ile Trp Ser Ile Gly Thr
 180 185 190
 Ile Phe Ala Glu Leu Ala Thr Lys Lys Pro Leu Phe His Gly Asp Ser
 15 195 200 205
 Glu Ile Asp Gln Leu Phe Arg Ile Phe Arg Ala Leu Gly Thr Pro Asn
 210 215 220
 Asn Glu Val Trp Pro Glu Val Glu Ser Leu Gln Asp Tyr Lys Asn Thr
 225 230 235 240
 20 Phe Pro Lys Trp Lys Pro Gly Ser Leu Ala Ser His Val Lys Asn Leu
 245 250 255
 Asp Glu Asn Gly Leu Asp Leu Leu Ser Lys Met Leu Ile Tyr Asp Pro
 260 265 270
 Ala Lys Arg Ile Ser Gly Lys Met Ala Leu Asn His Pro Tyr Phe Asn
 25 275 280 285
 Asp Leu Asp Asn Gln Ile Lys Lys Met
 290 295

30

<210> 9

<211> 1480

<212> DNA

<213> Homo sapiens

35

<220> CamKI

<223> Description of Sequence: N/A

<400> 9

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ctggctgtgg tcggggggca gtgggccatg ctgggggcag tgggaaggccc caggtggaag 180
5 caggcggagg acattagaga catctacgac ttccgagatg ttctgggcac gggggccttc 240
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gccaaaggagg ccctggaggg caaggaaggc agcatggaga atgagattgc tgcctgcac 360
aagatcaagc accccaacat tgtagccctg gatgacatct atgagagtgg gggccacctc 420
tacctcatca tgcagctggt gtcgggtggg gagctctttg accgtattgt ggaaaaaggc 480
10 ttctacacgg agcgggacgc cagccgcctc atcttccagg tgctggatgc tgtgaaatac 540
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ctggatgaag actccaaaat catgatctcc gactttggcc tctccaagat ggaggacccg 660
ggcagtgtgc tctccaccgc ctgtggaact ccgggatacg tggcccctga agtcctggcc 720
cagaagccct acagcaaggc tgtggattgc tgggccatag gtgtcatcgc ctacatcttg 780
15 ctctgcggtt accctccctt ctatgacgag aatgatgcca aactctttga acagattttg 840
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gagcagatca agaagaactt tgccaagagc aagtgggaagc aagccttcaa tgccacggct 1080
20 gtggtgcggc acatgaggaa actgcagctg ggcaccagcc aggaggggca ggggcagacg 1140
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25 ctctcactg cattttccat acaaagtgtt ctattttatt gttccttctt gtaataaagg 1440
gaagataaaa ccaaaaaaaaa aaaaaaaaaa acggaattcc 1480

<210> 10

30 <211> 370

<212> PRT

<213> Homo sapiens

<220>

35 <223> Description of Sequence: N/A

<400> 10

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			20				25						30			
	Glu	Val	Ile	Leu	Ala	Glu	Asp	Lys	Arg	Thr	Gln	Lys	Leu	Val	Ala	Ile
5			35				40					45				
	Lys	Cys	Ile	Ala	Lys	Glu	Ala	Leu	Glu	Gly	Lys	Glu	Gly	Ser	Met	Glu
		50				55					60					
	Asn	Glu	Ile	Ala	Val	Leu	His	Lys	Ile	Lys	His	Pro	Asn	Ile	Val	Ala
	65				70				75					80		
10	Leu	Asp	Asp	Ile	Tyr	Glu	Ser	Gly	Gly	His	Leu	Tyr	Leu	Ile	Met	Gln
			85					90					95			
	Leu	Val	Ser	Gly	Gly	Glu	Leu	Phe	Asp	Arg	Ile	Val	Glu	Lys	Gly	Phe
		100					105				110					
	Tyr	Thr	Glu	Arg	Asp	Ala	Ser	Arg	Leu	Ile	Phe	Gln	Val	Leu	Asp	Ala
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	Thr	Ala	Cys	Gly	Thr	Pro	Gly	Tyr	Val	Ala	Pro	Glu	Val	Leu	Ala	Gln
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	Lys	Pro	Tyr	Ser	Lys	Ala	Val	Asp	Cys	Trp	Ser	Ile	Gly	Val	Ile	Ala
25		195				200					205					
	Tyr	Ile	Leu	Leu	Cys	Gly	Tyr	Pro	Pro	Phe	Tyr	Asp	Glu	Asn	Asp	Ala
		210				215					220					
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	His	Pro	Trp	Ile	Ala	Gly	Asp	Thr	Ala	Leu	Asp	Lys	Asn	Ile	His	Gln
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<210> 12

<211> 424

<212> PRT

<213> Homo sapiens

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<220>

<223> Description of Sequence: N/A

<400> 12

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15

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25

30

Gly Ser Gly Ala Gln Gly Ile Val Cys Ala Ala Phe Asp Thr Val Leu

30

35

40

45

Gly Ile Ser Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Asn Gln

50

55

60

Thr His Ala Lys Arg Ala Tyr Arg Glu Leu Val Leu Leu Lys Cys Val

65

70

75

80

35

Asn His Lys Asn Ile Ile Ser Leu Leu Asn Val Phe Thr Pro Gln Lys

85

90

95

Thr Leu Glu Glu Phe Gln Asp Val Tyr Leu Val Met Glu Leu Met Asp

100

105

110

Ala Asn Leu Cys Gln Val Ile His Met Glu Leu Asp His Glu Arg Met
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 5 Ala Gly Ile Ile His Arg Asp Leu Lys Pro Ser Asn Ile Val Val Lys
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 Cys Thr Asn Phe Met Met Thr Pro Tyr Val Val Thr Arg Tyr Tyr Arg
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 Trp Ser Val Gly Cys Ile Met Gly Glu Leu Val Lys Gly Cys Val Ile
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 15 Phe Gln Gly Thr Asp His Ile Asp Gln Trp Asn Lys Val Ile Glu Gln
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 Asn Gly Val Val Lys Asp Gln Pro Ser Asp Ala Ala Val Ser Ser Asn
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 35 Ala Thr Pro Ser Gln Ser Ser Ser Ile Asn Asp Ile Ser Ser Met Ser
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<210> 13

<211> 3668

<212> DNA

<213> Homo sapiens

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<220> LIMK-2

<223> Description of Sequence: N/A

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<210> 14

<211> 638

5 <212> PRT

<213> Homo sapiens

<220>

<223> Description of Sequence: N/A

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<400> 14

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Trp His Gly Ser Cys Phe Arg Cys Ser Glu Cys Gln Asp Ser Leu Thr
      35              40              45
Asn Trp Tyr Tyr Glu Lys Asp Gly Lys Leu Tyr Cys Pro Lys Asp Tyr
      50              55              60
20 Trp Gly Lys Phe Gly Glu Phe Cys His Gly Cys Ser Leu Leu Met Thr
      65              70              75              80
Gly Pro Phe Met Val Ala Gly Glu Phe Lys Tyr His Pro Glu Cys Phe
      85              90              95
Ala Cys Met Ser Cys Lys Val Ile Ile Glu Asp Gly Asp Ala Tyr Ala
25              100             105             110
Leu Val Gln His Ala Thr Leu Tyr Cys Gly Lys Cys His Asn Glu Val
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Val Leu Ala Pro Met Phe Glu Arg Leu Ser Thr Glu Ser Val Gln Glu
      130             135             140
30 Gln Leu Pro Tyr Ser Val Thr Leu Ile Ser Met Pro Ala Thr Thr Glu
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Gly Arg Arg Gly Phe Ser Val Ser Val Glu Ser Ala Cys Ser Asn Tyr
      165             170             175
Ala Thr Thr Val Gln Val Lys Glu Val Asn Arg Met His Ile Ser Pro
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Gly Thr Pro Val Arg Thr Leu Arg Val Glu Glu Val Glu Asp Ala Ile

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	Leu Gly Lys Gly Phe Phe Gly Gln Ala Ile Lys Val Thr His Lys Ala		
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	His Pro Asn Val Leu Lys Phe Ile Gly Val Leu Tyr Lys Asp Lys Lys		
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	Leu Arg Ser Met Asp Pro Phe Pro Trp Gln Gln Lys Val Arg Phe Ala		
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	Lys Gly Ile Ala Ser Gly Met Ala Tyr Leu His Ser Met Cys Ile Ile		
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	Lys Arg Ala Pro Met Glu Lys Ala Thr Thr Lys Lys Arg Thr Leu Arg		
35	485	490	495
	Lys Asn Asp Arg Lys Lys Arg Tyr Thr Val Val Gly Asn Pro Tyr Trp		
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	Met Ala Pro Glu Met Leu Asn Gly Lys Ser Tyr Asp Glu Thr Val Asp		

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	Ile Phe Ser Phe Gly Ile Val Leu Cys Glu Ile Ile Gly Gln Val Tyr		
	530	535	540
	Ala Asp Pro Asp Cys Leu Pro Arg Thr Leu Asp Phe Gly Leu Asn Val		
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	Lys Leu Phe Trp Glu Lys Phe Val Pro Thr Asp Cys Pro Pro Ala Phe		
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	Phe Pro Leu Ala Ala Ile Cys Cys Arg Leu Glu Pro Glu Ser Arg Pro		
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10	Ala Phe Ser Lys Leu Glu Asp Ser Phe Glu Ala Leu Ser Leu Tyr Leu		
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	Gly Glu Leu Gly Ile Pro Leu Pro Ala Glu Leu Glu Glu Leu Asp His		
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	Thr Val Ser Met Gln Tyr Gly Leu Thr Arg Asp Ser Pro Pro		
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 <212> DNA
 <213> Homo sapiens

25 <220> PRK
 <223> Description of Sequence: N/A

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30 <211> 607

<212> PRT

<213> Homo sapiens

<220>

35 <223> Description of Sequence: N/A

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				515						520					525	
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<210> 17

<211> 3492

5 <212> DNA

<213> Homo sapiens

<220> PTP-SL

<223> Description of Sequence: N/A

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<400> 17

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 30 gctttcaatc ttcaagagcc aaaaaaaatt aaaataacta ccctcagcaa aactagctg 3420
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10 Asn Gln Lys Lys Ser Gly Lys Pro Val Phe Ile Tyr Lys His Ser Gln

35 40 45

Asp Ile Glu Lys Ser Leu Asp Ile Ala Pro Gln Lys Ile Tyr Arg His

50 55 60

Ser Tyr His Ser Ser Ser Glu Ala Gln Val Ser Lys Arg His Gln Ile

15 65 70 75 80

Val Asn Ser Ala Phe Pro Arg Pro Ala Tyr Asp Pro Ser Leu Asn Leu

85 90 95

Leu Ala Met Asp Gly Gln Asp Leu Glu Val Glu Asn Leu Pro Ile Pro

100 105 110

20 Ala Ala Asn Val Ile Val Val Thr Leu Gln Met Asp Val Asn Lys Leu

115 120 125

Asn Ile Thr Leu Leu Arg Ile Phe Arg Gln Gly Val Ala Ala Ala Leu

130 135 140

Gly Leu Leu Pro Gln Gln Val His Ile Asn Arg Leu Ile Gly Lys Lys

25 145 150 155 160

Asn Ser Ile Glu Leu Phe Val Ser Pro Ile Asn Arg Lys Thr Gly Ile

165 170 175

Ser Asp Ala Leu Pro Ser Glu Glu Val Leu Arg Ser Leu Asn Ile Asn

180 185 190

30 Val Leu His Gln Ser Leu Ser Gln Phe Gly Ile Thr Glu Val Ser Pro

195 200 205

Glu Lys Asn Val Leu Gln Gly Gln His Glu Ala Asp Lys Ile Trp Ser

210 215 220

Lys Glu Gly Phe Tyr Ala Val Val Ile Phe Leu Ser Ile Phe Val Ile

35 225 230 235 240

Ile Val Thr Cys Leu Met Ile Leu Tyr Arg Leu Lys Glu Arg Phe Gln

245 250 255

Leu Ser Leu Arg Gln Asp Lys Glu Lys Asn Gln Glu Ile His Leu Ser

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	Met Val Gln Pro Glu Gln Ala Pro Lys Val Leu Asn Val Val Val Asp		
5	290	295	300
	Pro Gln Gly Arg Gly Ala Pro Glu Ile Arg Ala Thr Thr Ala Thr Ser		
	305	310	315
	Val Cys Pro Ser Pro Phe Lys Met Lys Pro Ile Gly Leu Gln Glu Arg		
	325	330	335
10	Arg Gly Ser Asn Val Ser Leu Thr Leu Asp Met Ser Ser Leu Gly Asn		
	340	345	350
	Ile Glu Pro Phe Val Ser Ile Pro Thr Pro Arg Glu Lys Val Ala Met		
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	Glu Tyr Leu Gln Ser Ala Ser Arg Ile Leu Thr Arg Ser Gln Leu Arg		
15	370	375	380
	Asp Val Val Ala Ser Ser His Leu Leu Gln Ser Glu Phe Met Glu Ile		
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	Pro Met Asn Phe Val Asp Pro Lys Glu Ile Asp Ile Pro Arg His Gly		
	405	410	415
20	Thr Lys Asn Arg Tyr Lys Thr Ile Leu Pro Asn Pro Leu Ser Arg Val		
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	Cys Leu Arg Pro Lys Asn Val Thr Asp Ser Leu Ser Thr Tyr Ile Asn		
	435	440	445
	Ala Asn Tyr Ile Arg Gly Tyr Ser Gly Lys Glu Lys Ala Phe Ile Ala		
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	465	470	475
	Trp Gln Glu Asp Ser Pro Val Ile Val Met Ile Thr Lys Leu Lys Glu		
	485	490	495
30	Lys Asn Glu Lys Cys Val Leu Tyr Trp Pro Glu Lys Arg Gly Ile Tyr		
	500	505	510
	Gly Lys Val Glu Val Leu Val Ile Ser Val Asn Glu Cys Asp Asn Tyr		
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	Thr Ile Arg Asn Leu Val Leu Lys Gln Gly Ser His Thr Gln His Val		
35	530	535	540
	Lys His Tyr Trp Tyr Thr Ser Trp Pro Asp His Lys Thr Pro Asp Ser		
	545	550	555
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 580 585 590
 Gly Arg Thr Gly Cys Phe Ile Ala Thr Ser Ile Gly Cys Gln Gln Leu
 5 595 600 605
 Lys Glu Glu Gly Val Val Asp Ala Leu Ser Ile Val Cys Gln Leu Arg
 610 615 620
 Met Asp Arg Gly Gly Met Val Gln Thr Ser Glu Gln Tyr Glu Phe Val
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 Gln

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 agaaattgcc cagttgatgt cattgatcat caatactttc tactcgaaca aagagatctt 180
 tctgagagag ctcatttcaa attcatcaga tgcattggac aaaatccggt atgaaagctt 240
 gacagatccc agtaaattag actctgggaa agagctgcat attaacctta taccgaacaa 300
 30 acaagatcga actctcacta ttgtggatac tggaattgga atgaccaagg ctgacttgat 360
 caataacctt ggtactatcg ccaagtctgg gaccaaagcg ttcattggaag ctttgcaggc 420
 tgggtgcagat atctctatga ttggccagtt cgggtgttgg ttttattctg cttatttggt 480
 tgctgagaaa gtaactgtga tcaccaacaa taacgatgat gagcagtacg cttggggagtc 540
 ctcagcaggg ggatcattca cagtgaggac agacacaggt gaacctatgg gtcgtggaac 600
 35 aaaagttatc ctacacctga aagaagacca aactgagtac ttggaggaac gaagaataaa 660
 ggagattgtg aagaaacatt ctcagtttat tggatatccc attactcttt ttgtggagaa 720
 ggaacgtgat aaagaagtaa gcgatgatga ggctgaagaa aaggaagaca aagaagaaga 780
 aaaagaaaaa gaagagaaaag agtcggaaga caaacctgaa attgaagatg ttggttctga 840

tgaggaagaa gaaaagaagg atggtgacaa gaagaagaag aagaagatta aggaaaagta 900
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20

Ile Ile Asn Thr Phe Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu
35 40 45

25

Ile Ser Asn Ser Ser Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu
50 55 60

Thr Asp Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Leu
65 70 75 80

30

Ile Pro Asn Lys Gln Asp Arg Thr Leu Thr Ile Val Asp Thr Gly Ile
85 90 95

Gly Met Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys
100 105 110

35

Ser Gly Thr Lys Ala Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile
115 120 125

Ser Met Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val
 130 135 140

5 Ala Glu Lys Val Thr Val Ile Thr Lys His Asn Asp Asp Glu Gln Tyr
 145 150 155 160

Ala Trp Glu Ser Ser Ala Gly Gly Ser Phe Thr Val Arg Thr Asp Thr
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10 Gly Glu Pro Met Gly Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu
 180 185 190

Asp Gln Thr Glu Tyr Leu Glu Glu Arg Arg Ile Lys Glu Ile Val Lys
 195 200 205

15 Lys His Ser Gln Phe Ile Gly Tyr Pro Ile Thr Leu Phe Val Glu Lys
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Glu Arg Asp Lys Glu Val Ser Asp Asp Glu Ala Glu Glu Lys Glu Asp
 20 225 230 235 240

Lys Glu Glu Glu Lys Glu Lys Glu Glu Lys Glu Ser Glu Asp Lys Pro
 245 250 255

25 Glu Ile Glu Asp Val Gly Ser Asp Glu Glu Glu Glu Lys Lys Asp Gly
 260 265 270

Asp Lys Lys Lys Lys Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln Glu
 275 280 285

30 Glu Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp Asp Ile
 290 295 300

Thr Asn Glu Glu Tyr Gly Glu Phe
 35 305 310

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International Bureau(43) International Publication Date
21 November 2002 (21.11.2002)

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(10) International Publication Number
WO 02/093164 A3(51) International Patent Classification⁷: **A61K 31/506**,
G01N 33/68, C12Q 1/42, 1/48, C07K 16/40, C12N 15/11,
A61P 25/28, C07D 401/04, 409/14, 401/14, 471/04(74) Agents: **LEIDESCHER, Thomas et al.**; Zimmermann &
Partner, Postfach 330 920, 80069 München (DE).

(21) International Application Number: PCT/EP02/05420

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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
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(22) International Filing Date: 16 May 2002 (16.05.2002)

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60/293,528 29 May 2001 (29.05.2001) US
01117113.9 13 July 2001 (13.07.2001) EP
60/305,898 18 July 2001 (18.07.2001) US(84) Designated States (*regional*): ARIPO patent (GH, GM,
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European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
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19, 82152 Martinsried (DE).

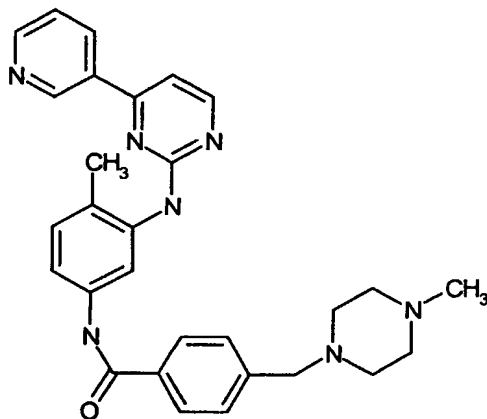
Published:

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BACHER, Gerald [DE/DE]; Kriegerstrasse 62, 82110
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ner Str. 184, 81371 München (DE).(88) Date of publication of the international search report:
4 September 2003*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: PYRIDYLPYRIMIDINE DERIVATIVES AS EFFECTIVE COMPOUNDS AGAINST PRION DISEASES



Compound 53 (Gleevec™)

(57) Abstract: The present invention relates to pyridylpyrim-
idine derivatives of the general formula (I) : wherein R
represents hydrogen or methyl and Z represents nitrogen
containing functional groups, the use of the pyridylpyrimidine
derivatives as pharmaceutically active agents, especially
for the prophylaxis and/or treatment of prion infections and
prion diseases, as well as compositions containing at least
one pyridylpyrimidine derivative and/or pharmaceutically
acceptable salt thereof. Furthermore, the present invention
is directed to methods for preventing and/or treating prion
infections and prion diseases using said pyridylpyrimidine
derivatives. Human cellular protein kinases, phosphatases and
cellular signal transduction molecules are disclosed as targets
for detecting, preventing and/or treating prion infections
and diseases, especially BSE, vCJD, or CJD, which can be
inhibited by the inventive pyridylpyrimidine derivatives.

WO 02/093164 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/05420

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/506 G01N33/68 C12Q1/42 C12Q1/48 C07K16/40 C12N15/11 A61P25/28 C07D401/04 C07D409/14 C07D401/14 C07D471/04		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZIMMERMANN J ET AL: "Phenylamino-pyrimidine (PAP) - derivatives: a new class of potent and highly selective PDGF-receptor autophosphorylation inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 11, 4 June 1996 (1996-06-04), pages 1221-1226, XP004134858 ISSN: 0960-894X table 1 <div style="text-align: center; margin-top: 20px;"> --- -/-- </div>	1, 2, 15, 16
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents:</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*8* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-size: 1.2em;">3 February 2003</div>		Date of mailing of the international search report <div style="text-align: center; font-size: 1.2em;">15. 05. 03</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-size: 1.2em;">Grassi, D</div>

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/05420

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZIMMERMANN J ET AL: "Potent and selective inhibitors of the Abl-kinase: phenylamino-pyrimidine (PAP) derivatives" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 2, 21 January 1997 (1997-01-21), pages 187-192, XP004135990 ISSN: 0960-894X table 1 ---	1,2,15, 16
X	ZIMMERMANN J ET AL: "PHENYLAMINO-PYRIMIDINE (PAP) DERIVATIVES: A NEW CLASS OF POTENT AND SELECTIVE INHIBITORS OF PROTEIN KINASE C (PKC)" ARCHIV DER PHARMAZIE, VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM, DE, vol. 329, no. 7, July 1996 (1996-07), pages 371-376, XP000885618 ISSN: 0365-6233 table I ---	1,2,15, 16
X	WO 95 09847 A (CIBA GEIGY AG ; ZIMMERMANN JUERG (CH)) 13 April 1995 (1995-04-13) cited in the application page 8, line 2; claim 1 page 13, line 1 ---	1-3,15, 16
X	EP 0 564 409 A (CIBA GEIGY AG) 6 October 1993 (1993-10-06) cited in the application claim 1 ---	1,2,15, 16
Y	JIMI T ET AL: "HIGH LEVELS OF NERVOUS SYSTEM-SPECIFIC PROTEINS IN CEREBROSPINAL FLUID IN PATIENTS WITH EARLY STAGE CRUTZFELDT-JAKOB DISEASE" CLINICA CHIMICA ACTA, AMSTERDAM, NL, vol. 211, no. 1/2, 15 October 1992 (1992-10-15), pages 37-46, XP002071132 ISSN: 0009-8981 page 37 page 40 ---	19,21, 26,42,43
Y	JAE-KWANG ET AL.: "Increased expression of CaM kinase II alpha in the brains of scrapie-infected mice" NEUROSCIENCE LETTERS, vol. 273, 1999, pages 37-40, XP002229677 abstract figure 1 page 39 ---	19,21, 26,42,43
	-/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/05420

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 64894 A (KANZAKI NAUYUKI ; MIWATASHI SEIJI (JP); OHKAWA SHIGENORI (JP); TAKE) 2 November 2000 (2000-11-02) page 12, line 1-8 -& EP 1 180 518 A 20 February 2002 (2002-02-20) page 1, line 5-8 page 12, line 1-8 ---	22-25
A	US 6 107 301 A (ALDRICH PAUL EDWARD ET AL) 22 August 2000 (2000-08-22) the whole document -----	3, 10, 17, 18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/05420

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1, 2, 15, 16
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
3, 10, 17, 18

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,15,16

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the independent claims 1, 2, 15, and 16 is impossible. Consequently, the search has been restricted to the use of the compounds for treating infectious diseases or neurodegenerative diseases (cf. claim 3).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 3,10,17,18

Use of compounds of formula (I) for the treatment of infectious diseases or neurodegenerative diseases.

2. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein FGF-R1: Use of compounds of formula (I) as inhibitors of FGF-R1, method for detecting prion disease by detecting activity of FGF-R1, method for preventing prion disease by applying an inhibitor of FGF-R1, method for regulating production of prions by applying an inhibitor of FGF-R1, monoclonal antibody binding to FGF-R1 etc.

3. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein Tkt: Use of compounds of formula (I) as inhibitors of Tkt, method for detecting prion disease by detecting activity of Tkt, method for preventing prion disease by applying an inhibitor of Tkt, method for regulating production of prions by applying an inhibitor of Tkt, monoclonal antibody binding to Tkt etc..

4. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein Abl: Use of compounds of formula (I) as inhibitors of Abl, method for detecting prion disease by detecting activity of Abl, method for preventing prion disease by applying an inhibitor of Abl, method for regulating production of prions by applying an inhibitor of Abl, monoclonal antibody binding to Abl etc..

5. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein clk1: Use of compounds of formula (I) as inhibitors of clk1, method for detecting prion disease by detecting activity of clk1, method for preventing prion disease by applying an inhibitor of clk1, method for regulating production of prions by applying an inhibitor of clk1, monoclonal antibody binding to clk1 etc..

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

6. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein MKK7: Use of compounds of formula (I) as inhibitors of MKK7, method for detecting prion disease by detecting activity of MKK7, method for preventing prion disease by applying an inhibitor of MKK7, method for regulating production of prions by applying an inhibitor of MKK7, monoclonal antibody binding to MKK7 etc..

7. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein LIMK-2: Use of compounds of formula (I) as inhibitors of LIMK-2, method for detecting prion disease by detecting activity of LIMK-2, method for preventing prion disease by applying an inhibitor of LIMK-2, method for regulating production of prions by applying an inhibitor of LIMK-2, monoclonal antibody binding to LIMK-2 etc..

8. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein CaM-KI: Use of compounds of formula (I) as inhibitors of CaM-KI, method for detecting prion disease by detecting activity of CaM-KI, method for preventing prion disease by applying an inhibitor of CaM-KI, method for regulating production of prions by applying an inhibitor of CaM-KI, monoclonal antibody binding to CaM-KI etc..

9. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein JNK2: Use of compounds of formula (I) as inhibitors of JNK2, method for detecting prion disease by detecting activity of JNK2, method for preventing prion disease by applying an inhibitor of JNK2, method for regulating production of prions by applying an inhibitor of JNK2, monoclonal antibody binding to JNK2 etc..

10. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein CDC2: Use of compounds of

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

formula (I) as inhibitors of CDC2, method for detecting prion disease by detecting activity of CDC2, method for preventing prion disease by applying an inhibitor of CDC2, method for regulating production of prions by applying an inhibitor of CDC2, monoclonal antibody binding to CDC2 etc..

11. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein PRK: Use of compounds of formula (I) as inhibitors of PRK, method for detecting prion disease by detecting activity of PRK, method for preventing prion disease by applying an inhibitor of PRK, method for regulating production of prions by applying an inhibitor of PRK, monoclonal antibody binding to PRK etc..

12. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein PTP-SL: Use of compounds of formula (I) as inhibitors of PTP-SL, method for detecting prion disease by detecting activity of PTP-SL, method for preventing prion disease by applying an inhibitor of PTP-SL, method for regulating production of prions by applying an inhibitor of PTP-SL, monoclonal antibody binding to PTP-SL etc..

13. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein PTP-zeta: Use of compounds of formula (I) as inhibitors of PTP-zeta, method for detecting prion disease by detecting activity of PTP-zeta, method for preventing prion disease by applying an inhibitor of PTP-zeta, method for regulating production of prions by applying an inhibitor of PTP-zeta, monoclonal antibody binding to PTP-zeta etc..

14. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein HSP86: Use of compounds of formula (I) as inhibitors of HSP86, method for detecting prion disease by detecting activity of HSP86, method for preventing prion disease by applying an inhibitor of HSP86, method for regulating production of prions by applying an inhibitor of HSP86, monoclonal antibody binding to HSP86

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

etc..

15. Claims: 13(part),19(part),21-26(part),31-37(part),
42-47(part)

Inventions related to protein GPIR-1: Use of compounds of formula (I) as inhibitors of GPIR-1, method for detecting prion disease by detecting activity of GPIR-1, method for preventing prion disease by applying an inhibitor of GPIR-1, method for regulating production of prions by applying an inhibitor of GPIR-1, monoclonal antibody binding to GPIR-1 etc..

INTERNATIONAL SEARCH REPORT

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International Application No

PCT/EP 02/05420

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